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Table of Contents

MANAGEMENT OF RHESUS-INCOMPATIBLE PREGNANCIES EMPLOYING AMNIOCENTESIS AND SPECTROSCOPIC EXAMINATION OF LIQUOR AMNII.

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THE problem of management of pregnancy in Rhesus-negative mothers who have developed anti-Rhesus agglutinins has been the source of considerable investigation and clinical trial. Bevis (1952) described a technique of examining specimens of liquor amnii for iron pigment by chemical methods, and later Bevis (1953, 1956 and 1960), by spectroscopic means, examined liquor amnii for blood pigments, methæmalbumin, oxyhæmoglobin and bilirubin. According to the relative amounts of pigments, bilirubin and oxyhæmoglobin, he was able to predict the outcome for the fœtus. This method of predicting the condition of the fœtus *in utero* has been used in addition to other pathological investigations, and this paper sets out a plan of management employing this technique.

Material.

The pregnancies which present the problem of management are those in which anti-Rhesus agglutinins are present when the patient's blood is examined early in pregnancy, or those in which anti-Rhesus agglutinins develop in the course of pregnancy.

In the former group the history of results of previous pregnancies is a guide to the optimum time for obtaining the first specimen of liquor amnii by abdominal amniocentesis. We have found that to attempt to take a sample before the thirtieth week is difficult and of no great advantage.

In the latter group we suggest that the patient's blood should be examined for the presence of anti-Rhesus agglutinins at the thirty-second week and abdominal amniocentesis should be performed as soon as possible after a positive result.

In the event of a negative result, the patient's blood should be tested again at 36 to 37 weeks in the usual way, but amniocentesis and spectroscopic examination of the liquor are not recommended at this stage, as the results are unreliable.

Method.

How to Obtain and Examine the Liquor.

We admit the patient to hospital for half a day and the bladder should be emptied immediately before the procedure. The abdominal amniocentesis is performed under local anæsthesia, through the anterior abdominal wall. If possible a site close to the mid-line between the umbilicus and symphysis pubis should be chosen. The direction of the puncture should be at a point between the anterior shoulder and the occipital bone of the fœtus.

A six-inch by 20 gauge needle is used, but occasionally it is found that the fine needle used for infiltrating the local anæsthetic punctures the membranes, and should this occur the specimen can be withdrawn without its being removed. Eight to 10 ml. of liquor amnii should be withdrawn for the examination, and it should be as free of blood as possible.

We take the precaution of observing the patient for two hours after the completion of the procedure.

Dangers which we try to avoid are puncture by the needle of the bowel, the bladder, or the baby's face or neck. The placenta is sometimes punctured, but apart from a small amount of blood being withdrawn into the needle, no trouble has ensued. Puncture of the cord or of a large placental vein near the root of the cord is probably the worst hazard, as the walls of these veins may not contract, but this has not occurred as far as we know.

Amniocentesis was performed just prior to planned Cæsarean section in a few cases and the uterine puncture site did not bleed.

The liquor amnii is centrifuged within two hours for 20 minutes at 6000 revolutions per minute, and may be examined then or it can be stored for up to 24 hours if this is necessary for transit purposes from the place of collection. If the specimen has been stored, it should be centrifuged again prior to its examination.

A "Unicam S.P. 600" spectrophotometer with 10 mm. cells is used for the examination, and the liquor amnii is subjected to wave lengths ranging from 700 mμ to 360 mμ. The corresponding units of absorption are plotted to give a graph (Figure I).

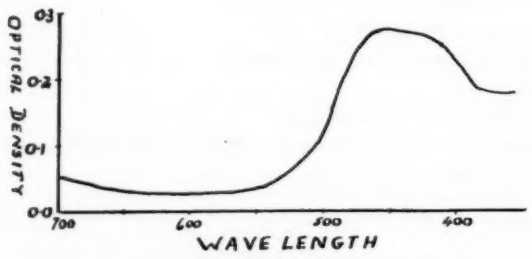

FIGURE I
Typical curve obtained with a Rhesus affected baby.

When is the Optimum Time for Amniocentesis?

Patients with a clear previous history and anti-Rhesus agglutinins appearing for the first time at 32 weeks should have a sample of liquor amnii obtained within two to three days. A second sample of liquor may be required in from seven to 14 days, depending on the result of the first examination.

Patients with a variable history of affected children and who have anti-Rhesus agglutinins present in their sera early in pregnancy should have a sample withdrawn at 30 to 32 weeks in the first instance. A subsequent sample will be required, the time interval depending on the result of the first specimen.

From the examinations of the amniotic fluid an accurate prognosis can be given on the condition of the fœtus, and its subsequent treatment can be determined.

Where should this Procedure be Carried Out?

Abdominal amniocentesis can be performed in any hospital under sterile conditions. The patient need be admitted for a few hours only, and should remain for two hours after the procedure.

When an affected fœtus is diagnosed, arrangements should be made to have the child born in a hospital where staff specially skilled in exchange transfusion can treat the baby.

Reasons for Employing Abdominal Amniocentesis.

Abdominal amniocentesis is the only reliable method at present of diagnosing (in utero) the Rhesus-negative fœtus of a heterozygous husband, and in such cases no further treatment is required.

The test also gives a more accurate indication of the progress of the disease than can be obtained by blood testing.

Furthermore, it can save patients who will subsequently deliver Rhesus-negative fœtuses the expense and family disturbance of being transferred to larger centres for confinement.

Results.

Since February, 1960, 100 specimens of liquor amnii have been examined. These have been obtained from patients at the Women's Hospital, Crown Street, Sydney, and from private patients, and have included specimens of liquor sent to us from country areas.

Forty-six amniocenteses have been attempted (of which 43 were successful) on 28 patients with Rhesus-incompatible pregnancies.

The remaining specimens were collected by artificial rupture of the membranes with a Drew Smythe catheter, and include specimens from cases of toxæmia, diabetes mellitus, chronic nephritis, multiple pregnancy and previous intrauterine death of unknown ætiology. These specimens have been examined to assess the reaction of liquor amnii to other stress conditions of the fœtus, and will be the subject of a later paper.

The results of prognosis in the Rhesus-incompatible pregnancies are set out in Table I.

Discussion.

Abdominal amniocentesis is a diagnostic procedure to be used in selected cases of suspected Rhesus incompatibility. It is not a substitute for the other pathological investigations now carried out.

It is the only reliable method at present of diagnosing the Rhesus-negative child of a heterozygous husband who has had previously affected children.

Provided due care is taken and conditions are sterile, the risk to the mother and child from the procedure is minimal and the value of the information gained is great.

Whenever possible two abdominal amniocenteses are performed, as a more accurate determination of the progress of the hæmolytic disease may be made.

Table II is a guide to the time interval between the collection of specimens of liquor amnii.

When the results of two specimens of liquor amnii are available, Table III indicates the approximate interval before delivery should take place.

In addition to the peak of the graph, the shape of the curve, the base-line level and the rate of change are taken into consideration when the prognosis is determined.

The base line, taken between 700 mμ and 600 mμ, should be between 0·06 and 0·02 unit of absorption; and the curve should be convex upwards between 520 mμ and 460 mμ.

Conclusions.

Abdominal amniocentesis employed in selected cases at the appropriate time can be a most useful adjuvant to the diagnosis and the subsequent treatment of Rhesus incompatibility.

One specimen of liquor amnii can indicate in the majority of cases whether the fœtus is affected or not. A second specimen will give an accurate indication of the rate of progress of the disease, and the probable outcome.

When the diagnosis has been established it is most important that an affected fœtus should be born in hospital where facilities for treatment are adequate.

Table I.
Reliability of Prognosis in Rhesus-Incompatible Pregnancies.

	Severity of Hæmolytic Disease.					
	Rhesus-Negative Fœtus.	Mild.	Mild to Moderate.	Moderate.	Moderate to Severe.	Severe.
Number of cases estimated from amniocentesis	2	8	5	3	6	2
Actual number of cases[1]	3	6	6	3	5	3

[1] Two patients are unconfined.

Summary.

1. The place of abdominal amniocentesis in the diagnosis and treatment of Rhesus-incompatible pregnancies is described.

2. The technique of amniocentesis and a suggested plan of management are described.

Table II.
Recommended Time Intervals between Amniocenteses.

Maximum Optical Density of Liquor Amnii at 30–32 Weeks.	Time Interval Before Second Amniocentesis.
0·10 or less	4 weeks
0·10 to 0·15	3 weeks
0·15 to 0·20	2 weeks
0·20 to 0·25	10 days
0·25 to 0·30	7 days
More than 0·30	7 days

3. The results of a small series of cases are given and these show that a very accurate prognosis can be given in the individual case.

Table III.
Prognostic Guide and Recommended Time of Delivery.

Units of Optical Density of Liquor Amnii (Maximum).		Rhesus Factor.	Recommended Time for Delivery of Baby.	Remarks.
First Estimation.	Second Estimation.			
0·4 or more	0·4 or more	Severe.	Immediately.	Probably hydrops fœtalis; doubtful extrauterine survival.
0·35	0·4 or more	Severe.	Immediately.	Salvageable fœtus.
0·3	0·3 to 0·35	Moderately severe.	7 to 10 days later.	Approximately 33 to 34 weeks' gestation.
0·25	0·25 to 0·3	Moderately severe.	10 to 14 days later.	Approximately 34 to 35 weeks' gestation.
0·2	0·2 to 0·25	Moderate.	2 weeks later.	Approximately 36 weeks' gestation.
0·15	0·15 to 0·2	Mild.	3 weeks later.	Approximately 37 weeks' gestation.
0·15	0·15	Very mild.	By 38th week.	

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We wish to thank Professor B. T. Mayes and Associate Professor R. Shearman for the facilities afforded us at the Queen Elizabeth Institute for Mothers and Babies at Sydney University, and the chairman and members of the honorary medical staff of the Women's Hospital, Crown Street, Sydney, for permission to obtain specimens from their patients.

References.

Bevis, D. C. A. (1952), "The Antenatal Prediction of Hæmolytic Disease of the Newborn", *Lancet*, 1: 395.

Bevis, D. C. A. (1953), "The Composition of Liquor Amnii in Hæmolytic Disease of the Newborn", *J. Obstet. Gynæc. Brit. Emp.*, 60: 244.

Bevis, D. C. A. (1956), "Blood Pigments in Hæmolytic Disease of the Newborn", *J. Obstet. Gynæc. Brit. Emp.*, 63: 68.

Bevis, D. C. A. (1960), personal communications.

ALCOHOLIC OFFENDERS IN A VICTORIAN PRISON.

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Of 11,910 men committed to Pentridge Goal, Melbourne, in 1959, 4059 (35%) were "alcoholic offenders" — that is, they were charged with being "drunk and disorderly"[1] (3892 or 33%) or "drinking methylated spirits"[2] (203 or 2%) (Whatmore, 1959). Psychiatric investigation of such individuals has recently been facilitated by the establishment of a clinic in this Victorian prison.

While other studies (Christiansen, 1951; Morris, 1951; Scott, 1944; Schmidt, 1951) have been performed in an attempt to show the interrelationship between alcoholic intake and alcoholism on the one hand, and crime on the other, the aim of the present studies has been to investigate those persons whose "crime" is essentially that of drinking alcohol. Before the study of their criminal backgrounds, life histories, alcoholic patterns and admission status was undertaken, it was considered mandatory to isolate any characteristics differentiating them from "serious offenders" who, together with vagrants and other petty offenders, comprise the rest of the prison population. Accordingly a two-stage investigation was undertaken. During the first stage prison records and social backgrounds of "alcoholic" and "serious" offenders were compared in an endeavour to detect differentiating factors; in the second stage a profile of the alcoholic offenders was built up from clinical material and prison records.

Method of Investigation.

"Alcoholic offenders" was taken to denote those individuals shown in the prison register as convicted of being "drunk and disorderly" or of "drinking methylated spirits". "Serious offenders" connoted prisoners convicted of other crimes such as "breaking and entering", without regard to their use or abuse of alcohol; these men were all serving sentences for a duration of longer than six months. Data were obtained from prison documents, in addition to physical and psychiatric examinations made of alcoholic offenders. Psychiatric examinations consisted of individual interviews, each lasting some 45 minutes.

One hundred alcoholic offenders were chosen from prisoners admitted in the last quarter of 1959. Of the psychiatric examinations that were performed it was possible to employ material from only 65 interviews, the number being restricted by the repeated appearance of certain prisoners in the period selected, and by others having received extremely short sentences. Further, the organic impairment demonstrated by some patients precluded them from contributing information of value to the investigation.

One hundred and thirteen "serious offenders" who appeared consecutively before the Classification Committee of the Victorian Penal Department in the second quarter of 1959 formed a group for comparison. Each prisoner was interviewed for about 20 minutes; the material was combined with that obtained from prison records and compared with the data obtained from the alcoholic offenders.

[1] *Police Offences Act (Vic.)*, No. 6337, Sect. 24, 1958.
[2] *Poisons Act (Vic.)*, No. 6336, Sect. 64 and 69, 1958.

A Comparison of "Alcoholic" and "Serious" Offenders.

Tables I, II and III demonstrate that striking differences exist between the groups of alcoholics and the serious offenders studied in the investigation. It will be noted that the two groups are quite dissimilar in regard to their ages at their first and most recent convictions, the number of previous gaol sentences served, their living arrangements and their past and present marital situations.

It will be observed from Table I that, in contrast to the alcoholics, the vast majority of the serious offenders were convicted for the first time before the age of 21 years. The alcoholics received their convictions later in life, by which time first convictions in serious offenders were rare. Similarly, as judged by their age at their most recent conviction, the serious offenders were a much younger group of individuals; 95% were under 40 years of age when convicted, whereas 83% of the alcoholic offenders were over 40 years of age.

Table II shows the alcoholic offenders to be "repeaters"; this term denotes a specific kind of recidivist. Thus no less than 44% had served more than 50 previous gaol sentences, many of them lasting only a few days. On the other hand 70% of the serious offenders had served two previous gaol sentences or less; the longer length of their gaol sentences and their younger age structure made it impossible for them to become "repeaters" like the alcoholics, and in this way to accumulate enormous numbers of brief sentences.

The alcoholic offenders, it is clear from Table III, were living prior to their convictions in far less settled conditions than their serious offender counterparts. They had fewer family ties, any attachments which had led to residence with a marital partner having been broken before their present conviction.

A Profile of Alcoholic Offenders.

It was possible to construct a psychiatric profile covering the majority of alcoholic offenders studied from 18 features subsumed under their criminal records, life histories, alcoholic patterns and statuses on admission.

Criminal Record.

Five features were apparent in the criminal records of the alcoholic offenders. The first was the long-term span of convictions. More than half the alcoholic offenders had received their sentences during a period in excess of 10 years. The second was the large number of convictions. Almost half had more than 50 convictions. One in five had over 100 convictions. Only three were first offenders. The mounting rate of convictions was the third feature apparent. In individual cases the incidence of convictions often showed a progressive acceleration over the years. Fourthly, there were unusually long sentences. Nearly half had served total sentences of from two to five years; more than one in six had been imprisoned for a total period of over five years, usually in sentences of only a few days each. The fifth feature was the infrequency of concurrent crime. Involvement in serious crime was rare. Although nearly one-quarter of the offenders had been convicted of felonies at some time, this was usually many years before the onset of the existing alcoholic pattern.

Life History.

Six salient features were found in the life histories of the alcoholic offenders. The first feature was the broken home. Over one-third of the subjects reported parental separation, or death of one or both parents before the age of 21 years. One in seven said that they had been in institutions during childhood. The second feature was a poor school record. Less than half stated they had got beyond the sixth grade at school, although there was no evidence on clinical examination that their intelligence was lower than average. The third feature was the low work level. One-quarter had never been employed other than as casual labourers, and only one-third had ever been in skilled work. The fourth feature concerned unusual mobility. Only one-half reported that they had ever stayed in one place continuously for five years or more. More than a third stated that, from the age of 21 years onwards, they had never stayed in one place in continuous employment for longer than a year. At the time of conviction almost three-quarters had no fixed address. The fifth feature was the rarity of lasting marital relationships. Only one-quarter of the subjects stated that they had ever had a marital relationship (whether legal or *de facto*) which had lasted for five years or more, although over half the sample said they had been involved in one, or often more than one, such relationship of shorter duration. Over one-third stated that they had never lived with a woman as man and wife. The sixth feature was the lack of hobbies and other recreations. One in five subjects said that they had never been even casual participants in dancing, sporting activities or indeed any social activities whatsoever apart from those incidental to drinking.

TABLE I.

Ages of Alcoholic and Serious Offenders at First and Most Recent Convictions.

	Alcoholic Offenders.	Serious Offenders.
Age at first conviction:		
Under 21 years	5 (7%)	87 (77%)
21 to 40 years	37 (49%)	24 (21%)
Over 40 years	33 (44%)	2 (2%)
Age at most recent conviction:		
Under 21 years	0 (0%)	41 (36%)
21 to 40 years	13 (17%)	66 (59%)
41 to 60 years	49 (66%)	6 (5%)
Over 60 years	13 (17%)	0 (0%)

TABLE II.

Number of Previous Gaol Sentences Served by Alcoholic and Serious Offenders

Number of Previous Gaol Sentences.	Alcoholic Offenders.	Serious Offenders.
None	3 (4%)	46 (41%)
1 or 2	5 (7%)	33 (29%)
3 to 9	7 (9%)	32 (28%)
10 to 49	27 (36%)	2 (2%)
50 to 99	18 (24%)	0 (0%)
100 or more	15 (20%)	0 (0%)

Alcohol Pattern.

Five features characterized the alcoholic offenders with regard to the alcoholic pattern. The first of these was that drinking was established in adolescence. More than two-thirds of the subjects stated that they had begun drinking before the age of 21 years; one in seven admitted that alcohol was a problem before they were 21 years of age, while in two-thirds of the remainder, alcohol was obviously a problem by the time they were 40 years of age. Compulsive patterns of drinking were in evidence. In one-third of the subjects, the total waking activities revolved around the consumption of alcohol, any work performed being purely casual and carried out to facilitate the purchase and consumption of alcoholic beverages. A further one-third were chronically excessive drinkers who apparently enjoyed social activities in association with their continuous preoccupation with alcohol. Of the remainder, half were periodic drinkers who worked industriously, and sometimes abstained completely between bouts; the other half were rarely inebriated and showed no deterioration in their working habits or social relationships from an originally poor level. For the last-mentioned individuals, taking alcohol only constituted a problem in that it was frequently associated with arrest and conviction. A third feature was the consumption of methylated spirits. Nearly half the subjects admitted that they had drunk methylated spirits at one time or another. There was, fourthly, a lack of insight into the alcoholic problem. Almost half claimed that alcohol did them no harm and stated that they could "give it away tomorrow" if they so desired. Less than one

in five felt that alcohol was a severe problem to them, about which they should take some action or on account of which they required help. Fifthly, there was an evident disinterest in securing treatment. Two-thirds of the subjects said they were not interested in Alcoholics Anonymous; only two declared they had ever attended meetings regularly. Two-thirds had had at least one admission to a mental hospital.

Medical Status on Admission.

Two main features were apparent when the alcoholic offenders were admitted to prison. One was physical ill-

TABLE III.

Living Arrangements and Marital Situations of Alcoholic and Serious Offenders.

Most Recent Living Arrangements.	Alcoholic Offenders.	Serious Offenders.
Living with relatives or friends	5 (8%)	86 (76%)
Living alone	12 (18%)	21 (19%)
No fixed address	48 (74%)	6 (5%)
Married (legally or by common law in past)	38 (58%)	41 (36%)
Living with spouse (legal or de-facto) at present	0 (0%)	29 (26%)

ness. Of 70 patients, five were acutely physically ill on admission, for example, with pneumonia or heart failure. Twenty-one others needed urgent medical attention for conditions such as unstabilized epilepsy, fractures and incipient delirium tremens; seven had long-standing physical diseases such as chronic bronchitis. There was little evidence of gross vitamin deficiency among the subjects; but only 37 of the 70 were in good physical health. Poor dental conditions were also found. From an orthodontic standpoint, one-third of the subjects were completely edentulous, while a further one-third had only one or two natural teeth. Fewer than one in ten were "dentally satisfactory"—that is, possessing adequate teeth or serviceable dentures.

Discussion.

Alcoholic offenders admitted to prison represent a pressing community problem, whether the situation is looked at socially, medically or economically.

From a social standpoint, since alcoholic offenders (as has been demonstrated) differ very much from serious offenders, the practice of locking them up with serious criminals is both unjust and illogical. Despite the fact that the sentences the alcoholic offenders receive are usually of only a few days' duration, these periods of detention have to be served in maximum security prisons built and administered to detain serious criminals who are serving long sentences. In such prisons there is no therapeutic programme suitable for alcoholic offenders, who have perforce to spend their daytime hours in the remand yard or on the prison farm. Their only specific therapy is a weekly meeting of Alcoholics Anonymous, at which attendance is voluntary; medical and dental attention consists merely of a routine examination by an orderly and, if necessary, emergency treatment.

From a medical standpoint it cannot be claimed, in view of the high rate of recidivism, that the existing method of management is effective. Although the fear of punishment or the actual experience of conviction and serving a sentence may be a deterrent to many individuals, it appears that after the alcoholic offender has served one or two sentences the experience has no corrective effect on his subsequent pattern of behaviour. Indeed the opposite effect is often produced; observation suggests that many chronic offenders look forward to their next "visit" to prison, where they can obtain food and shelter while waiting for pensionary and social benefits to mount sufficiently to provide them with funds for further drinking on their release.

From an economic standpoint the present method of handling the problem is quite expensive. To keep a man in Pentridge Prison for a week costs £10 10s. To this amount must be added the costs arising from an arrest, a court appearance and the preparation of documents and records by both the police and the penal departments. In addition to this direct expense to the community there is the expense of maintaining charitable institutions to provide alternative accommodation for alcoholics. Further, there is the financial loss from the incapacitation of an appreciable section of the labour force, in addition to the Social Service benefits which alcoholics receive.

In view of the fact that most alcoholic offenders appear never to have made an adequate adjustment at any time, the ineffectiveness of the present method of management is not surprising. Alcoholics are always difficult to treat effectively and those who spend appreciable proportions of their lives in gaol are amongst the most difficult therapeutic problems. For many of these alcoholic offenders, alcohol, once a symptom of poor adjustment, has over the passage of time become the principal and indeed the only way in which they obtain any satisfaction out of life; often it has become a convenient escape from the oppression of unpleasant circumstances. Not only have they become habituated to this type of behaviour for many years, even resorting to the use of methylated spirits when there is no other alcohol available, but they have little appreciation of any other way of meeting their needs, or of the deleterious effects of alcohol on their bodily health. They have no interest in treatment and lack social contacts which might be of assistance in their rehabilitation.

In view of these considerations the prognosis must remain guarded, whatever the treatment régime. Nevertheless it would appear that a prolonged period of continuous treatment utilizing all available psychiatric and social services, followed by a gradual return to the community with special provision for after-care, would offer the best prospect of lasting results (Cade, 1956; Hansen and Teilmann; 1954; Richards, 1957; Selzer, 1958). Such a programme, in order to limit access to alcohol, would have to provide for enforced detention under conditions of security; but, despite this, its orientation would be therapeutic rather than custodial. Its cost need not be prohibitive. Such a programme has been undertaken and favourably reported on by Brightman (1960), and is recommended by, amongst others, Morris (1960) and Reckless (1955). The latter suggests that when special courts are being set aside to deal with specific problems, such as traffic offences, the problem of the alcoholic offender might be considered sufficiently great as to warrant special consideration.

There is already in Victoria statutory provision for sentences of up to 12 months' imprisonment for any person convicted of being an "habitual drunkard", but it is rarely invoked. Only six convictions were made under the Act in 1959 (Whatmore, 1959)[3]. Similarly, the provision for the committal of "inebriates"[4] is at present in abeyance, since no licensed centres are currently gazetted. Nevertheless, the Victorian Penal Department has achieved considerable advances in their management of both serious and juvenile offenders, and the Mental Hygiene Authority has demonstrated its willingness to collaborate in planning treatment programmes for offenders. It is reasonable to anticipate therefore that, in the course of time, appropriate action will be taken to provide adequate care for these unfortunate individuals who today are so repeatedly committed to prison as "alcoholic offenders". Despite their instability and social isolation, these members of society require sympathy, skilled treatment and adequate supervision.

Summary.

1. The findings of two investigations conducted into alcoholic offenders at Pentridge Gaol, Melbourne, during 1959 are presented.

2. Data are produced which suggest that alcoholic offenders differ from serious offenders in terms of their age at their first and most recent convictions, the number of previous gaol sentences served, and in their living arrangements and marital situations. So marked are these

[3] *Police Offences Act (Vic.)*, No. 6337, Sect. 69, 1958.

[4] *Inebriates Act (Vic.)*, No. 6278, 1958.

differences that it appears that alcoholic offenders and serious offenders require different types of management.

3. From a detailed scrutiny of criminal records, life histories, alcoholic patterns and medical statuses on admission, a profile of the alcoholic offenders is constructed.

4. The problem of the alcoholic offender is briefly discussed and the suggestion is made that present methods of management are socially inappropriate, therapeutically ineffective and economically wasteful. An alternative programme of compulsory treatment with adequate after-care is suggested as a practical approach promising the most lasting results.

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References.

BRIGHTMAN, I. J. (1960), "The Future of Alcoholism Programs". Public health report, U.S. Department of Health, Education and Welfare, LXXV, 9: 775.

CHRISTIANSEN, K. (1951), unpublished data, quoted by Schmidt, in "European Seminar and Lecture Course on Alcoholism", W.H.O., Copenhagen: 54.

CADE, J. F. J. (1956), "Alcohol, a Community Responsibility", MED. J. AUST., 1: 363.

HANSEN, H. A., and TEILMANN, K. (1954), "A Treatment of Criminal Alcoholics in Denmark", *Quart. J. Stud. Alcohol*, 15: 246.

MORRIS, N. (1951), "The Habitual Criminal", Longmans, London.

MORRIS, N. (1960), "Alcoholism in Relation to Crime and Punishment", Foundation for Research and Treatment of Alcoholism, Sydney: 152.

RECKLESS, W. C. (1955), "The Crime Problem", Appleton Century Crofts, New York.

RICHARDS, W. (1957), "The Psychology of Alcoholism", MED. J. AUST., 2: 544.

SCHMIDT, M. (1951), "European Seminar and Lecture Course on Alcoholism", W.H.O., Copenhagen: 55.

SCOTT, G. M. (1944), "Alcoholism and Criminal Behaviour", in "Mental Abnormality and Crime", edited by Leon Radzinowicz and J. W. C. Turner, Macmillan, London, 2: 167.

SELZER, M. L. (1958), "On Involuntary Hospitalization of Alcoholics", *Quart. J. Stud. Alcohol*, 19: 660.

WHATMORE, E. (1959), "Report of Director of Penal Services", Victorian Papers.

A CONTROLLED EVALUATION OF "LIBRIUM" IN THE TREATMENT OF ALCOHOLICS.

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THE problem of treating the alcoholic is one of considerable interest at the present time when there is an ever-increasing concern being taken in the problems posed by such persons. Many therapeutic techniques have been tried — protective drugs such as "Antabuse" or "Dipsan", conditioning programmes, psychotherapy, "inspirational and hortatory methods" (Tappan, 1960) that include such organizations as Alcoholics Anonymous and the Salvation Army; various drugs of sedative-tranquillizer type, endocrines and, no doubt, many others. In all probability the best results are obtained by using more than one technique (Bartholomew, 1961*a*), but this paper is only concerned with endeavouring, in a small way, to evaluate the value or otherwise of a new drug, "Librium" (7-chloro-2-methyl-amino-5-phenyl-3H-1,4 benzodiazapine-4-oxide hydrochloride), whose structure is shown schematically below.

"Librium" has been hailed as a drug of value in the treatment of alcoholics by Speight (1960), Lawrence (1960) and Lawrence *et alii* (1960), whilst Vogt (1961) suggests that the drug is "quite effective in a wide range of mental disorders where severe anxiety is present". This statement by Vogt has been echoed by a number of authorities (Breitner, 1960; Constant, 1960; English, 1960; Farb, 1960; Harris, 1960; Kinross-Wright *et alii*, 1960; Robinson, 1960; Sussex, 1960; Thomas, 1960; Ticktin and Schultz, 1960; Tobin *et alii*, 1960; Walzer *et alii*, 1960; Denham, 1960;

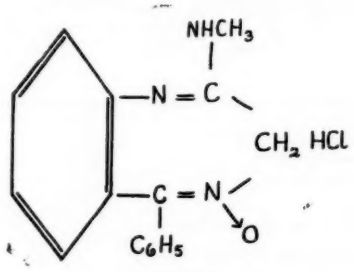

FIGURE I.
Structural formula of "Librium".

Fullerton and Bethell, 1960; Kagan, 1960; Vergano, 1960; Todd, 1960). Smith (1960), as a result of a controlled trial, concluded: "Chlordiazepoxide was found to be an effective agent for the relief of anxiety and tension with an associated improvement in social behaviour." On the other hand, a number of clinicians are far less impressed with the efficacy of "Librium" (Ingram and Tinburg, 1960; Lindsay, 1960; Fitzpatrick, 1960; Cade, 1961; Stoller, 1961). Of much greater importance than these conflicting opinions voiced by clinicians is the fact that "Librium" has been hailed in the lay Press as being of the greatest value in the treatment of alcoholism (Barnes, 1960). The position has arisen where, within a few months of the drug being on the Australian market, and before it has been even roughly evaluated, a member of the House of Representatives (Kearney, 1960), in putting a question to the Minister for Health, stated:

> Can the Minister affirm that rather distinctive success has been claimed for the drug ["Librium"] in both America and the United Kingdom as an effective cure for alcoholics . . . will he take steps to have it included in the list of free drugs under the Pharmaceutical Benefits Act?

Before any drug can be considered even reasonably evaluated, many clinical trials (preferably controlled) are needed using different populations, different dosage schedules and under a variety of conditions. This article reports the results of "Librium" being given under controlled conditions to a series of alcoholics attending an out-patient clinic.

Method.

Every alcoholic (an individual whose main complaint related to alcohol) who came to the clinic and was examined by one of us was treated in the normal manner as indicated by his physical and mental state; his history was taken, he was physically examined, his mental state was appraised and he was interviewed by a social worker and put in touch with Alcoholics Anonymous. Those that required hospitalization were sent to the appropriate Receiving House. Those patients that were to be treated on an out-patient basis were divided into two groups on the basis of suitability or otherwise for inclusion in the experimental population. Those not considered suitable were: (i) persons suffering from severe physical disabilities such as cirrhosis of the liver and gross cerebral pathology; (ii) persons considered psychotic; (iii) persons unable to speak adequate English for easy communication; and (iv) those patients who indicated that they would not cooperate, and did not really want any treatment unless it suited them. Such patients often refuse medicines and do not return regularly to the clinic as requested. One patient, an epileptic, was to have been included in the investigation, but was finally excluded as it was not possible to match him.

Those patients selected to take part in the investigation were all given one week's supply of a placebo that was identical with "Librium", and this was followed by a further month when the patients continued taking the same number of capsules, either the active drug or placebo.

All patients were matched in pairs in terms of five criteria; one of the pair received the active drug whilst the other was in receipt of the placebo, the evaluating clinician not being appraised of which patient was on the drug. The five criteria for matching were: (i) sex; (ii) age; (iii) type of drinking problem, such as chronic alcoholism, periodic drinking, heavy drinking and anxiety in remitted alcoholics; (iv) type of work—categorized into casual, artisan and office; (v) whether or not the patient was living permanently with his/her spouse (*de facto* or *de jure*). This matching was not unduly difficult, as about 150 new cases of alcoholism are seen each month, and the majority of sufferers are males who are aged between 30 and 50 years and are either casual workers or artisans. The reason for this double blind technique was that it was intended at the outset to evaluate the drug by means of a sequential analysis (Bross, 1952; Sainsbury and Lucas, 1959; Emmerson and Sandilands, 1961).

The dosage used was one or two capsules three times a day (30 or 60 mg. of the active drug daily). Such a dose was chosen as it compares with that prescribed by Speight (1960) and was below 100 mg. daily, which dose appears to lead to an increased incidence of side-effects (Vogt, 1961). It was arranged so that alternate pairs received the smaller or the larger dose. The period of the investigation was five weeks — one week with placebo followed by four weeks with either drug or placebo.

Every patient was evaluated regarding the effect of the "treatment" in terms of four factors that were themselves rated on a somewhat arbitrary scale. The factors and their ratings were: (i) physical appearance — the same or worse; improved; much improved; (ii) alleged drinking — the same or more; drinking, but less; not drinking; (iii) work record — remaining the same; improved (either obtained a job or better at it); markedly improved (this category was in part assessed by the pay packet the patient would often bring to the clinic, and the females that were housewives were rated on how they ran the house and dealt with the children); (iv) sense of tension or anxiety — the same; less; much less.

As far as possible the initial story told by the patient, and the claims made regarding improvement under treatment were verified whenever possible. This was achieved in a number of cases by interviewing relatives, most often the wives.

Throughout the investigation the patients were given no other pharmacological preparations, but were encouraged to attend meetings of Alcoholics Anonymous, attend the clinic for supportive psychotherapy, and take advantage of the possible help available from the social workers. "Antabuse" or "Dipsan" was not given, as it has been found that some tranquillizers tend to block the effect of these two substances in the presence of alcohol (Goldberg, 1961). As it was not known whether or not "Librium" would prove to be a blocking agent, it was thought better to leave these protective drugs out of the total régime during the period of the investigation.

Results.

Forty patients (20 pairs) were initially involved, but seven ceased attending the clinic during the investigation, so that the final evaluation was concerned with 33 patients and 14 pairs (in one case both members of a pair were lost). The forty patients included six females, and the data concerning the sex, age, dosage of the drug or placebo, type of drinking, type of work and marital status of the whole group is set out in Table I, as well as the response shown by each patient after the month's régime.

Of the 14 pairs that continued for the whole of the month's treatment (one patient ceased taking the active drug after five days due to side effects, but is considered here as "completing the whole investigation period") three demonstrated no difference at all between the active drug and placebo (Pair I on six capsules per day and Pairs VI and VIII on three capsules per day), whilst a further six pairs could only just be distinguished (Pairs IV, X, XII, XVI and XVIII on the smaller dosage and Pair XIII on the larger), so that nine pairs out of the thirteen do not support any claims as to the efficacy of "Librium". The remaining four pairs were thought to be so little different as between response to drug and placebo that it was unreasonable to state that the drug was better than placebo or vice versa.

Of the six pairs that did not last for the month of the investigation two were broken owing to patients on placebo not returning (Pair XVII taking six capsules per day and Pair XX taking three capsules per day). Three pairs were broken by patients receiving "Librium" not returning (Pairs IX, XV and XIX, all receiving the larger dosage). Pair XI was lost owing to both patients' failure to return to the clinic.

One pair was broken (Pair VII) when the patient in receipt of 60 mg. of the active drug refused further medication after five days owing to unpleasant side-effects that included marked drowsiness, some mild extrapyramidal signs and symptoms, and a degree of impotence.

Of the 33 patients that remained at the end of the month there was not one that had not improved to some extent. Many were still drinking, but all stated that they felt much better than for many months. The patient that gave up the drug on account of side effects after five days was considerably improved after a month as the result of general supportive measures.

As the drug is alleged to be of great value in anxiety and tension states it is of interest to note the ratings under the heading of "Tension" in Table I. Of the 32 patients remaining after the month's trial (the patient on the active drug in Pair VII being excluded) seven did not notice any difference in their state of tension or anxiety as the result of treatment; four of these were in receipt of the drug and three of them were having the larger dose. Five patients maintained, and gave the impression, that their tension and anxiety were "much less". Two of these were receiving the active drug, one 30 mg. the other 60 mg. daily. Twenty patients considered they were less tense, of which nine were in receipt of "Librium" and only one was taking the larger dose. The patient taking "Librium" in Pair VII, who gave up taking the drug, stated that he felt much less tense whilst receiving the medication, but that he had been reduced to the point of having little interest in life.

It has been stated that "Librium" removes the desire to drink. This was investigated in the 33 patients of this series and the answer in general terms was that the drug had no effect at all. The majority of the patients said at some time or other that they "had absolutely no interest in drink" or "no desire to drink", but would later say what an effort it had been to stay away from drink. The drug was in no way more effective than placebo in producing an alleged disinterest in alcohol. No patient who had continued to drink, or who had suddenly started again, made any comment that supported the findings of Speight (1960) to the effect that the patients on "Librium" would only partially finish their drink, as they could analyse the situation and decide they could manage without alcohol.

Speight (1960) comments upon the rapidity of action of "Librium, and notes that the action of the drug may be manifest in from 10 to 15 minutes. Such is not our experience as, on the contrary, the patients in this series often did not report on any improvement for periods of over a week. What did quite often occur was that the patients would remark that they felt a great deal better and more relaxed after having had an opportunity for a talk with a person prepared to listen and who was sympathetic.

Side-effects are an important matter to consider when one is evaluating a drug. It may be that the side-effects are so frequent, so marked and so typical that a simple double blind is of no value as a controlled technique (Holdway, 1960). In this investigation very few side-effects were noted, and in only one case were the side-effects of sufficient severity to cause the cessation of therapy. The

TABLE I.
Data Regarding the Forty Patients in the Investigation.

Case Number.	Pair Number.	Dose per Day.	Sex.	Age. (Years.)	Drinking Problem.[2]	Type of Work.	Marital Status.	Physical Condition.	Amount of Drinking.	Performance in Work.	Tension.
1	I	60 mg.	F.	36	CA	O	S.	No change.	Less.	No change.	Less.
2		60 mg.[1]	F.	32	CA	O	S.	No change.	Less.	No change.	Less.
3	II	30 mg.	F.	42	H	H/W	M.	No change.	Less.	No change.	Less.
4		30 mg.[1]	F.	49	H	H/W	M.	No change.	None.	Improved.	Much less.
5	III	60 mg.	F.	39	CA	H/W	M.	No change.	Less.	Improved.	Much less.
6		60 mg.[1]	F.	45	CA	H/W	M.	No change.	None.	No change.	Much less.
7	IV	30 mg.	M.	36	H	Cas	S.	Improved.	None.	No change.	Less.
8		30 mg.[1]	M.	35	H	Cas	S.	No change.	None.	No change.	Less.
9	V	60 mg.	M.	54	CA	O	S.	No change.	Less.	Improved.	No change.
10		60 mg.[1]	M.	51	CA	O	S.	Improved.	None.	No change.	Less.
11	VI	30 mg.	M.	50	CA	O	M.	No change.	None.	Improved.	Less.
12		30 mg.[1]	M.	47	CA	O	M.	No change.	None.	Improved.	Less.
13	VII	60 mg.	M.	43	CA	A	M.	Refused drug after five days owing to side-effects.			
14		60 mg.[1]	M.	44	CA	A	M.	No change.	None.	No change.	Much less.
15	VIII	30 mg.	M.	38	P	O	M.	No change.	None.	No change.	Less.
16		30 mg.[1]	M.	42	P	O	M.	No change.	None.	No change.	Less.
17	IX	60 mg.	M.	49	CA	A	S.	Did not continue attendance at clinic.			
18		60 mg.[1]	M.	45	CA	A	S.	Improved.	None.	No change.	No change.
19	X	30 mg.	M.	54	CA	A	S.	No change.	None.	No change.	Less.
20		30 mg.[1]	M.	52	CA	A	S.	No change.	Less.	No change.	Less.
21	XI	60 mg.	M.	49	CA	Cas	S.	Did not continue attendance at clinic.			
22		60 mg.[1]	M.	53	CA	Cas	S.	Did not continue attendance at clinic.			
23	XII	30 mg.	M.	47	DA	A	M.	No change.	None.	No change.	Much less.
24		30 mg.[1]	M.	41	DA	A	M.	No change.	None.	No change.	Less.
25	XIII	60 mg.	M.	60	CA	Cas	S.	Improved.	Less.	No change.	No change.
26		60 mg.[1]	M.	59	CA	Cas	S.	Improved.	Less.	No change.	Less.
27	XIV	30 mg.	M.	36	CA	Cas	S	Improved.	None.	Improved.	Less.
28		30 mg.[1]	M.	39	CA	Cas	S.	No change.	None.	No change.	Less.
29	XV	60 mg.	M.	47	P	Cas	S.	Did not continue attendance at clinic.			
30		60 mg.[1]	M.	45	P	Cas	S.	No change.	None.	No change.	No change.
31	XVI	30 mg.	M.	29	CA	O	M.	No change.	None.	No change.	Less.
32		30 mg.[1]	M.	25	CA	O	M.	No change.	None.	No change.	No change.
33	XVII	60 mg.	M.	29	P	O	S.	Improved.	None.	No change.	No change.
34		60 mg.[1]	M.	31	P	O	S.	Did not continue attendance at clinic.			
35	XVIII	30 mg.	M.	42	DA	A	M.	No change.	None.	Much improved.	Less.
36		30 mg.[1]	M.	47	DA	A	M.	No change.	None.	No change.	Less.
37	XIX	60 mg.	M.	39	H	Cas	S.	Did not continue attendance at clinic.			
38		60 mg.[1]	M.	36	H	Cas	S.	No change.	None.	No change.	Less.
39	XX	30 mg	M.	43	H	O	M.	No change.	None.	No change.	No change.
40		30 mg.[1]	M.	47	H	O	M.	Did not continue attendance at clinic.			

[1] Placebo given in place of the active drug.

[2] Drinking problem: H = heavy drinking; CA = chronic alcoholism or alcoholic addiction; P = periodic heavy drinking ("benders"); DA = "dry alcoholism" or remitted alcoholism.

Type of work: A = artisan work; O = office work including "professions"; Cas = casual work; H/W = housework.

side-effects reported to date are drowsiness (by nearly every author), sudden falling asleep (Bartholomew, 1961c), and extrapyramidal signs and symptoms, particularly ataxia (by most authors), whilst excessive gain in weight, acute rage reactions and loss of libido are noted among a number of others by Tobin *et alii* (1960). In this series 17 patients complained of some tiredness or lethargy, but 10 of these were receiving placebo; two patients taking the active drug complained of mild headache and one of these commented upon some dizziness and blurred vision; and three patients receiving placebo complained of nausea and one stated the "drug" made him very constipated.

Discussion.

This investigation is admittedly small and very limited in its scope, and a great deal more research will be needed before the true value of "Librium" can be properly assessed. The reason for such precipitous publication is simply to draw attention to our quite contrary impressions and findings when the published work of Speight (1960) and Lawrence *et alii* (1960) is considered and to correct any false impressions gained from the sensational publicity given the drug in the lay Press.

The problems of the alcoholic have to be fully appreciated in a trial of this type. It is our experience that the vast majority of alcoholics who come to the clinic with any intention of accepting treatment, and who return a week later, are tremendously improved — this without any specific therapeutic endeavour. Most such people come in with remorse, or full of self-pity after a shock — as, for example, their family leaving them — and they stay away from alcohol for a short time. In this period they improve physically and very often their mental state shows evidence of a return to an earlier and more normal status. If any drug, "Librium" or otherwise, is given in this period then it will be credited with an effect that is really due to a complex of factors. It was for this reason that all the patients in this series had the first week on placebo in order that the trial with the drug should be started when the initial non-specific improvement had taken place. This precaution was not taken by Speight (1960), and is one of the gross weaknesses of his paper.

The method of evaluating the changes in the patients in this investigation is by no means as satisfactory as would be wished. It is admitted that the ranking on a three-point scale of four factors is both arbitrary and over-simple. However, as has been stated, this report is concerned only with first impressions gathered with some concern regarding bias and the need for controlled investigation. It does not pretend to be a really sophisticated assessment of a new drug. However, it is submitted that the four factors used represent the type of improvement the clinician is really concerned with and therefore they are quite suitable for this type of investigation.

The results indicate that in the dosage used "Librium" has no effect that can be clearly distinguished from those of a placebo. The alcoholics all improved over the period of a month, whether on 30 mg. or 60 mg. of "Librium" daily or placebo. The drug had no specific effect on anxiety or tension, no effect on the desire to drink and no rapid action. Among those patients who did not keep in touch with the clinic during the investigation the drug and placebo were nearly equally represented.

As has been noted, the design of the investigation was produced in order that (i) it should be blind and (ii) that the results should be analysed sequentially by the statistical technique known as sequential analysis. In the event such was found to be unsuitable in that the results produced by the drug did not differ sufficiently from those seen following the administration of placebo. In other words, a series of "ties" resulted that could not be scored. For this reason the matched-pair double-blind technique was used but the sequential analytic plan was not implemented.

Unfortunately the series is too small to allow the various subgroups of alcoholics to be analysed in terms of response to "Librium", but inspection of Table I suggests that the active drug was no better than placebo for any of the drinking categories.

An interesting aspect of the investigation was the real value the patients placed upon the capsules. Many have been very loath to give up taking their "drug" since the end of the study. One patient, taking placebo, thought the capsules were both very effective and attractive.

A very real problem with alcoholics in our experience has been the patient's giving up the taking of alcohol only to take instead a variety of drugs (James, 1960, 1961; Bartholomew, 1961*a*, *b*). As far as could be ascertained there was no evidence that any of the 33 patients who continued the trial were taking any other medication, with the possible exception of a sedative at night. However, since the investigation has ended and some of the patients have been taken off "Librium" or placebo, there have been two alcoholics who have returned intoxicated with drugs—in one case "Relaxa-tabs" and in the other phenobarbitone. It would seem that many patients such as these need to feel they are taking something that is psychopharmacologically effective (the drug-dependent personality described by James, 1960) and that attraction plays a large part in forming a belief as to efficacy.

This communication is not intended to suggest that "Librium" is of no value in the armamentarium of the physician and psychiatrist. Such a suggestion would be presumptuous in view of the findings of other investigators and the words of Hoffman and Steiger (1961), who write:

> Drugs do not affect patients merely by pharmacologic or physiologic action. Equally important are the beneficial or harmful effects consequent upon the emotional meaning of the physician's prescription. . . . Drugs effective in the therapeutic milieu of the mental hospital may not be beneficial in an out-patient department.

Apart from this Lawrence *et alii* (1960) draw attention to two of their findings that suggest lines for further research. They note firstly that "there is a wide range of individual variation in the dose required for a therapeutic effect", and secondly "there also appears to be a critical minimal dosage level below which therapeutic effects disappear completely". Thus the position is still quite uncertain as to the true value of "Librium", and no dogmatic statements can in truth be made unless of very limited application. This article intends only to record the fact that in this series, over a period of a month, in the dosage used, the drug was not distinguishable from placebo.

Summary.

"Librium" is a new drug that has been alleged to be of value in the treatment of anxiety states and alcoholism.

A double blind investigation involving 40 alcoholic patients is reported.

In doses up to 60 mg. daily "Librium" was found to be indistinguishable from placebo over a period of one month.

Side effects were very few, and only one patient refused to continue taking the drug for this reason.

The importance of a controlled technique has been alluded to with special reference to the non-specific improvement to be expected in alcoholics over the first week of treatment.

Acknowledgements.

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References.

BARNES, D. (1960), "New Pill Stops This (and Quietens Tigers)", *Australasian Post*, November 17: 20.

BARTHOLOMEW, A. A. (1961*a*), "The Problem of Alcoholism", MED. J. AUST., 1: 109

BARTHOLOMEW, A. A. (1961*b*), "Intoxication and Habituation to Glutethimide ('Doriden')", MED. J. AUST., 3: 51.

BARTHOLOMEW, A. A. (1961*c*), "A Dramatic Side-Effect of a New Drug—'Librium' ", MED. J. AUST., 2: 436.

BREITNER, C. (1960), "Drug Therapy in Obsessional States and Other Psychiatric Problems", *Dis. nerv. Syst.*, 21: 31.

BROSS, I. (1952), "Sequential Medical Plans", *Biometrics*, 8: 188.

CADE, J. F. (1961), private communication.

CONSTANT, G. A. (1960), "Preliminary Report on the Use of a New Agent in Depression and Tension States", *Dis. nerv. Syst.*, 21: 37.

DENHAM, J. (1960), "Side-Effects of 'Librium' ", *Lancet*, 2: 875.

EMMERSON, B. T., and SANDILANDS, P. A. (1961), "A Clinical Trial of 'Mecoral', An Hypnotic Tablet Containing Chloral Hydrate", MED. J. AUST., 1: 243.

ENGLISH, D. O. (1960), " 'Librium', a New Non-Sedative Neuroleptic Drug: A Clinical Evaluation", *Curr. ther. Res.*, 2: 88.

FARB, H. H. (1960), "Experience with 'Librium' in Clinical Psychiatry", *Dis. nerv. Syst.*, 21: 27.

FITZPATRICK, E. (1961), private communication.

GOLDBERG, L. (1961), private communication.

HARRIS, T. H. (1960), "Methaminodiazepoxide", *J. Amer. med. Ass.*, 172: 1162.

HOFFMAN, F. H., and STEIGER, W. A. (1961), "Use of Symptomatic Drugs", *Modern Medicine of Australia*, 4: 114.

HOLDWAY, V. (1960), "Trial of 'Imipramine' ", *J. ment. Sci.*, 106: 1443.

INGRAM, I. M., and TIMBURG, G. C. (1960), "Side-Effects of 'Librium' ", *Lancet*, 2: 766.

JAMES, I. P. (1960), "Addiction to Hypnotics", *Brit. med. J.*, 1: 1504.

JAMES, I. P. (1961), "Alternating Addiction to Alcohol, Carbromal and Other Drugs", MED. J. AUST., 1: 326.

KAGAN, G. (1960), "Side-Effects of 'Librium' ", *Lancet*, 2: 876.

KEARNEY, V. D. (1960), reported in MED. J. AUST. (1961), 1: 69.

KINROSS-WRIGHT, F. E., COHEN, I. M., and KNIGHT, J. A. (1960), "The Management of Neurotic and Psychotic States with Ro 5-0690 ('Librium')", *Dis. nerv. Syst.*, 21: 23.

LAWRENCE, F. E. (1960), "Some Recent Avdances in the Medical Management of Alcoholism", read to the Academy of General Practice, Chicago, Illinois.

LAWRENCE, F. E., JOHNSON, J. M., WEBSTER, A. P., and SCHWARTZ, L. (1960), "Chlordiazepoxide in the Treatment of Alcoholism", *J. Neuropsychiat.*, 2: 93.

LINDSAY, J. B. S. (1960), private communication.

ROBINSON, R. C. V. (1960), "Adjunctive Therapy of Dermatoses with Librium", *Dis. nerv. Syst.*, 21: 43.

SAINSBURY, P., and LUCAS, C. J. (1959), "Sequential Methods Applied to the Study of Prochlorperazine", *Brit. med. J.*, **2: 737.**

SMITH, M. E. (1960), "A Comparative Controlled Study with Chlordiazepoxide", *Amer. J. Psychiat.*, 117: 362.

SPEIGHT, P. H. (1960), "Notes on the Use of 'Librium' in the Treatment of Alcoholism", MED. J. AUST., 2: 741.

STOLLER, A. (1961), private communication.

SUSSEX, J. N. (1960), "The Use of 'Librium' in Office Treatment of Mixed Neurotic States", *Dis. nerv. Syst.*, 21: 53.

THOMAS, L. J. (1960), "Preliminary Observation on the Use of 'Librium' (Ro 5-0690) in Internal Medicine", *Dis. nerv. Syst.*, 21: 40.

TICKTIN, H. E., and SCHULTZ, J. D. (1960), " 'Librium', A New Quietening Drug for Hyperactive Alcoholic and Psychotic Patients", *Dis. nerv. Syst.*, 21: 49.

TOBIN, J. M., BIRD, I. F., and BOYLE, D. E. (1960), "Preliminary Evaluation of 'Librium' (Ro 5-0690) in the Treatment of Anxiety Reactions", *Dis. nerv. Syst.*, 21: 11.

TODD, J. (1960), 'Side-Effects of "Librium" ', *Lancet*, 2: 1090.

VERGANO, J. B. (1960), "Side-Effects of 'Librium' ", *Lancet*, 2: 876.

VOGT, A. H. (1961), "Methaminodiazepoxide ('Librium') in Chronic Refractory Anxiety", *Amer. J. Psychiat.*, 117: 743.

WALZER, R. S., KINLAND, M. L., and BRAUN, M. (1960), "A Clinical Trial of Methaminodiazepoxide ('Librium')", *Amer. J. Psychiat.*, 117: 456.

THE OXYGEN CONTENT OF ANÆSTHETIC MIXTURES.

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IT is important that those who administer anæsthetics should be aware of the principles governing the control of oxygen percentage in the anæsthetic mixture that is delivered to the alveoli of the patient. Otherwise hypoxic and near hypoxic anæsthetics can be administered.

Those who may be aware of the apparent content of oxygen leaving the anæsthetic machine may yet not be cognizant of the percentage of gas that the patient is actually inhaling.

This may be due to several factors and not all can be detailed now. Much has been written on the ill effects and causation of carbon dioxide build-up in anæsthetic circuits and the emphasis has, for the time, been removed from other parameters. Hypercarbia is certainly insidious in its approach and detrimental in its effect, but the same may be said of hypoxia. The function of respiration is to remove carbon dioxide and to obtain oxygen; consideration of the two can never be separated.

Where there is rebreathing of exhaled atmosphere, apart from the toxic effect of carbon dioxide on the patient, there will be depletion of oxygen from an ultimately inadequate supply of oxygen, and the excess carbon dioxide will further displace oxygen from the circuit. Another reason, it would appear, for these hypoxic mixtures being used, is the habit, presumably for economic reasons, of utilizing what has become known as minimal flow of gases.

I will attempt to enumerate briefly the main factors influencing the oxygen percentage, and also the actual percentage one is likely to meet with the various anæsthetic techniques in common use.

Method.

Percentages of oxygen that are quoted without reference have been obtained by means of a Beckman paramagnetic oxygen analyser which was generously lent by the Royal Alexandra Hospital for Children, Sydney. With rapid respiratory rates it is impossible to obtain immediate samples of gases with the hand pump of the apparatus. The resistance of gas passing through the fine connecting tubing of the sampling needle and the silica gel allowed the bellows to fill relatively slowly. Continuous monitoring could not be performed because fluctuations in gas pressure produced movement of the mirror and no certain reading could be achieved. Further, it required some two samples of gas completely to change the gas in the silica gel bottle, tubing and analysing chamber. However, if the hand bulb was compressed and allowed to fill in a controlled manner with the operator's fingers on the bulb, it was possible to obtain samples of gas in any required phase of respiration, although at times that sample might consist of gas from two cycles, but of the same phase of respiration. The figures quoted represent a range of recordings from 5 to 20, depending a good deal upon the duration of the anæsthetic. For each such recording quoted in this paper there probably would be 2 to 4 readings of the analyser, because check readings were made constantly.

Unless specifically stated or portrayed in a graph, the figures reproduced represent recordings made after 15 to 20 minutes from the commencement of the anæsthetic, sufficient time having been allowed for stabilization and, in particular, denitrogenation. This allowed the optimum conditions for oxygen to be in the circuit.

Before each series of investigations the apparatus was checked for accuracy by the use of 100% nitrous oxide, 100% oxygen and again by the indrawing of air. The apparatus can be read to the order of accuracy of 1%, and is also calibrated in tensions of gas (millimetres of mercury).

"Open" Ether.

With the open administration of ether, the oxygen concentration beneath the mask was found to range from 15% while ether was dripping to 19% when no ether was being added. The ambient temperature was 23°-24° C. This only confirms Faulconer's work of 1947, in which an average concentration of 14% was commonly found, and the lowest was 10·5%.

The addition of small flows of oxygen not sufficient to disperse large volumes of anæsthetic vapour can abolish this hypoxic state without disturbing the plane of anæsthesia.

A child, aged 2 years and weighing 26 pounds, was the subject of the information in Figure I. As premedication he received pentobarbitone (1 grain) and atropine (0·4 mg.) and the anæsthetic consisted of ethyl chloride and ether. When respiratory depression was greatest, the oxygen inhaled, sampled from well within the oro-pharyngeal airway, was also in greatest concentration at a time when it was most needed. (The oxygen catheter was fixed along the nose and was not in contact with the airway.) When the minute volume increased after the cessation of the administration of ether, the oxygen concentration of the inhaled gas was lower.

Open Circuit.

In the open circuit the following apparatus was used: an Ayre's T-piece with an open limb; a Y tube; a Pickens perforate pipe.

Provided there is no dilution of the anæsthetic mixture being delivered to the patient by the patient's inhaling of air, the percentages of gas delivered and gas inhaled are the same. This requires large flows of gases, and Ayre and Inkster have shown that, in fact, it requires a gas flow some three times the minute volume to prevent the inhalation of air.

This type of apparatus is reserved for infants, in whom the minute volume is small and the total flow of gases is also consequently small.

The Ayre's T-piece is variously modified to economize in gas flow. Ayre himself uses an extension to the open limb and maintains that there will be no rebreathing, provided that the capacity of the extension is not more than one-third of the tidal air, and that the flow of fresh gas is one and a half times to twice the minute volume. The difficulty here, of course, is that the tidal air (minute volume) is not often constant throughout the anæsthetic procedure.

With Jackson Rees' modification, it is estimated that there will be no rebreathing when the total flow of fresh gas is greater than twice the minute volume of the patient.

Under certain conditions, such as high rates of ventilation with controlled respiration, and using Jackson Rees' technique, it is theoretically possible to allow rebreathing. This also occurs with controlled respiration using the Magill circuit (Sykes). This is compensated for by frequent emptying of the bag and refilling of it with fresh gas. When high percentages of oxygen are being utilized the decrease in oxygen percentage will be negligible. It has been found that with halothane as the agent and oxygen as the vehicle, a 98% oxygen atmosphere is being inspired. It is also probable that, with controlled respiration, the minute volume is greater than that found when the patient is breathing voluntarily, and upon which the fresh gas flow has been calculated.

With voluntary respiration, the reservoir bag in Jackson Rees' technique acts as an expiratory flap valve, and, during inspiration, there may be insufficient gas to satisfy the demand of maximum inspiratory flow. It is better, in these circumstances, to remove the bag and leave the corrugated tubing as an extended limb. The volume contained in the corrugated breathing tube in common use is 80 ml. and this will often be greater than one-third of the tidal air as stipulated by Ayre. If this modification of the technique is used, fresh gases at least three times the estimated minute volume will be required.

Little investigation has been done to measure the minute volume or the maximum inspiratory flows of children, and even less for infants. An attempt was made to do this by using a flap of a wisp of cotton wool over the open limb of the T-piece. The fresh gas flow was adjusted so that, in inspiration with spontaneous breathing, the flap of cotton wool was not pulled onto the open limb.

As an example of this investigation (to be published later): an infant, aged 18 months, had a maximum inspiratory flow of 12 to 15 litres per minute when "Trilene" and nitrous oxide were being administered, and a maximum inspiratory flow of 6 litres per minute with halothane under similar conditions of premedication and surgery. Similarly, infants aged six weeks had a maximum

inspiratory flow of 9 litres per minute with "Trilene", and of 2 to 6 litres per minute with halothane and oxygen as the anæsthetic.

Such variations in maximum inspiratory flow give an indication of the variation in minute volume.

Adriani has shown that in older children, aged 4 to 8 years, with ether anæsthesia there is an increase in the minute volume over that found in the unpremedicated, unanæsthetized patient.

Complete studies of the minute volume of children are usually based on the work of Hall, in which little indication is given of the precise conditions of premedication and anæsthesia under which the figures were obtained. The two examples quoted by Hall were of subjects anæsthetized

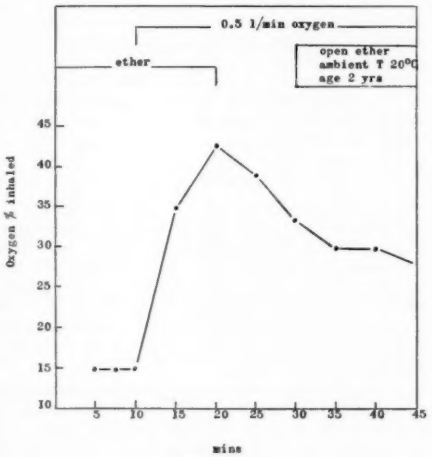


FIGURE I.

Oxygen concentration of inhaled gas during the administration of an "open" ether anæsthetic. The subject was aged two years and the ambient temperature was 20° C.

with thiopentone given rectally, nitrous oxide, oxygen and ether. If these figures are taken as standards, gas flows considered to be a function of minute volume may not be sufficient to prevent rebreathing.

Minute volume in the anæsthetized patient is dependent on the nature of the premedication, the agents in use and the depth of anæsthesia existing at the time when the particular type of surgery is being performed. Calculation of fresh gas flows to prevent rebreathing must take these factors into consideration. A comparison of other investigations in this field shows that there is an enormously wide range of figures for minute volume in the various age groups.

Non-Rebreathing Valves.

In systems with non-rebreathing valves (for example, Rubens) there is no rebreathing provided the valves do work satisfactorily. Rebreathing will occur if the moisture of the exhaled gas condenses on the valve seats and the valve sticks. The percentage of gas inhaled is the same as that delivered by the fresh flow of gases (Figure II). A decrease or increase in the size of the reservoir bag, which must always be in the circuit, will indicate whether the total flow is adequate or not. With this method, the minute volume can be accurately and constantly observed and covered by the fresh flow of gases.

Air-Ether Mixtures from Vaporizers.

Ikezomo *et alii* have shown that marked falls in the oxygen saturation of hæmoglobin occur when ether and air are being administered from a vaporizer (for example, the E.M.O. type) if, for any reason, pulmonary ventilation is depressed. Such oxygen percentage decreases in the inhaled mixture are in direct proportion to the amount of ether vapour inhaled. Their investigation showed that the range of oxygen was from 140 to 145 mm. of mercury (18%) and that considerable falls occurred with spontaneous breathing.

Controlled respiration provided adequate oxygen, but assisted respiration with such a system was never effective in the production of sufficient oxygenation.

Semi-Closed Circuits.

With a circuit such as that of Magill (Mapleson's A), in which the reservoir bag is near the anæsthetic machine and the exhalation valve close to the patient, the concentration of the oxygen inhaled by the patient is that calculated from the flows being delivered (Figure II).

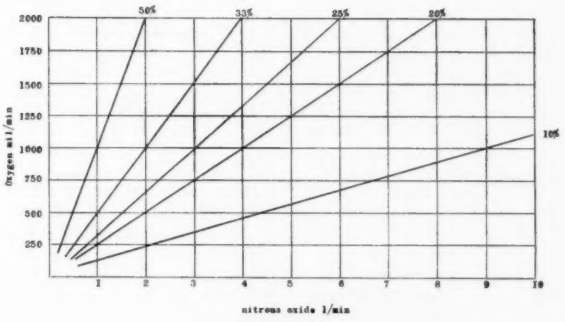


FIGURE II.

Graph showing percentages of delivered oxygen calculated from gas flows.

For this statement to be true it is presumed that (i) the patient is not rebreathing; (ii) the flowmeters or percentage regulators are accurate; (iii) no adjuvant volatile agents are being used.

Rebreathing.

Mapleson has shown that, if it is assumed that there is no longitudinal mixing of fresh gas and exhaled gas, if the total flow delivered is equal to the minute volume, there will be no rebreathing other than that of dead space gas.

Harrison and others have shown that there may be mixing, and that 0·53 volume *per centum* of carbon dioxide can be detected at the proximal end of the corrugated tube. This will not greatly affect the concentration of oxygen, the theme of this paper.

However, Micklem and Jones maintain that, in such a system over an observed period, there is a difference of 2·3% at 20 minutes and 2·5% at 30 minutes between the oxygen percentage at the proximal end of the corrugated tube and that under the mask. They suggest that it was due to an accumulation of carbon dioxide. This difference has also been observed by myself in children being anæsthetized with nitrous oxide, oxygen and "Trilene", the period of observation being extended for 85 minutes. When a mask was used, the corrugated tubing and mask became an extension of the dead space. However, there was a constant difference in the oxygen percentages of the mask atmosphere and the corrugated tube, measured in samples taken 4 cm. from the expiration valve, indicating that not all the dead space gas was passing up the tube, but rather that there was mixing in the distal end of the corrugated tube. Mixing probably occurs because maximum expiratory flow exceeds the total flow of fresh gas produced by delivery of fresh gas by the anæsthetic machine and the flow produced by the tension of the reservoir bag, which is partly empty at the end of inspiration. When intubation was used in place of a mask, this variation in atmosphere was not seen if the minute volume was accurately estimated. In Figure III

there is considerable variation in the atmosphere with the lower flow of fresh gas. When the fresh gas flow (which was probably greater than the minute volume) was increased, the percentages of oxygen in the proximal and distal corrugated breathing tubing remained the same. It should also be noted that the oxygen content in the Magill tube remains below the delivered quantity. The Magill tube is an extension of the dead space of the subject, and this is an indication that the alveolar content of oxygen will be even less, as mixing occurs down the tracheo-bronchial alveolar tree. True expiratory samples showed a decrease in oxygen content of 1%. Samples of gas in the distal corrugated tube were taken 5 cm. from the expiratory valve.

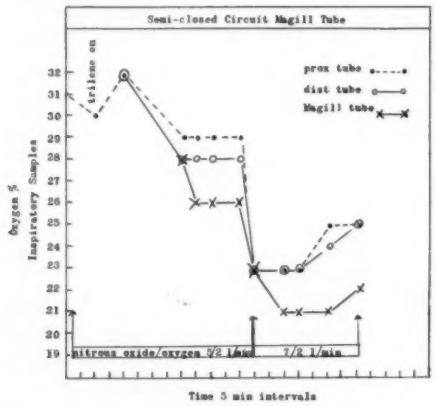


FIGURE III.

Percentage of inhaled oxygen estimated from inspiratory samples taken from various parts of a semi-closed circuit. Uninterrupted line with crosses indicates Magill tube. Uninterrupted line with circles indicates distal tube. Interrupted line with dots indicates proximal tube.

To prevent rebreathing in a semi-closed circuit several conditions are necessary: (i) the tidal air must be maximal, otherwise the dead space will be a considerable factor; (ii) the minute volume must be determined fairly accurately; and (iii) the dead space must be minimal.

The addition of higher flows of oxygen may restore the calculated oxygen content, but will not necessarily prevent the accumulation of carbon dioxide unless the total flows are equal to the minute volume of the patient at the time. Further, the accumulation of carbon dioxide will displace some of the added oxygen and may reform the original hypoxic mixture.

Flowmeters and Regulators.

It is recorded (Macintosh and Mushin) that, provided the rotameter type of flowmeters are vertical, they are extremely accurate.

Records were made (see Table I) of fresh gas delivered by several B.O.C. (Boyle's) anæsthetic machines at various flow rates, It is obvious that recorded percentages do not coincide with calculated percentages (Figure II). Fortunately, in most instances, the inaccuracy is in favour of an increased oxygen percentage delivered. Special note should be made of machines designated "E" and "F".

This excess oxygen percentage also occurs with oxygen and cyclopropane mixtures. As an example, machines "C" and "I", delivering 500 ml. per minute each of cyclopropane and oxygen, delivered 58% and 64% oxygen respectively.

Bourne and Hunter have independently shown that, with some gas machines (not identified) in use in England, the percentage of oxygen indicated on the dial had little relation to the actual percentage delivered. Some anæsthetic machines in common use for dental practice in this country were similarly investigated (Table II).

Adjuvant Volatile Agents.

We learn from Mapleson that the content of trichlorethylene delivered from a Boyle's bottle in a semi-closed circuit, provided the gas is not bubbled through the agent, ranges from 1% to 1·5% by volume.

Gusterson and Clark have shown that the Goldman vaporizer, for use with halothane, will not deliver a concentration greater than 3·5% by volume in a semi-closed circuit with flows of 3 litres per minute. This obtains in England, but caution should be exercised in this country, where the ambient temperature in our summer is often very high. In the true semi-closed circuit, as defined in this paper, with flows of 8 litres per minute, the maximum concentration obtainable is stated to be 2·2% by volume. An investigation of vaporizing ether from a Boyle's bottle in such a circuit is shown (Table III) in which the flows used early are commonly reversed for maintenance. The concentration of oxygen therefore in a semi-closed circuit will be reduced in direct proportion to the amount of volatile agent being vaporized. The concentration of oxygen may also be altered by these adjuvants changing the minute volume in respect to calculated fresh gas flows as described previously.

Closed Circuits.

With the administration of an anæsthetic in a closed circuit, provided that the basal oxygen consumption is replaced and that compensation is made for leaks, the oxygen content will depend on: (i) whether the nitrogen has been displaced from the patient and circuit; (ii) whether efficient carbon dioxide absorption is occurring; (iii) the content of the gaseous agent (cyclopropane being the only one employed in this circuit) or volatile agent being delivered.

It has been found that, after a thiopentone-succinylcholine induction and maintenance with ether, the content of oxygen varies from 36% to 94% on inspiratory sampling when the oxygen is being delivered at 0·5 to 1 litre per minute.

Closed Circuit with Spill.

This is sometimes referred to as a semi-closed circuit. In the true semi-closed circuit, no carbon dioxide absorption is utilized and the minute volume of the patient is matched with a fresh flow of gases. In the true closed circuit, the expiratory valve is firmly closed, small flows of fresh gas are used (commonly only basal oxygen requirements are supplied), and carbon dioxide absorption is retained. The use of the term "closed circuit with spill' will immediately identify this anæsthetic technique.

The oxygen content being delivered by the machine is that calculated from the exact flows in use (Figure II and Table I). However, the calculation of the oxygen content actually being inhaled by the patient in this type of circuit is complex. Fitton evolved a formula for such a calculation, but in his summary stated that his paper was wholly theoretical.

Woolmer has similarly propounded a formula. There are, of course, so many variables that, even if the flowmeters were accurate, it is not possible in practice to use any such formulæ. Woolmer states that approximations of such variables would introduce too many inaccuracies.

The variables are here enumerated so that there may be some understanding of the factors involved in the final determination of the oxygen content in the inhaled anæsthetic mixture. They are (i) oxygen lost by leakage, and consumed by the patient; (ii) total flows of fresh gases; (iii) nitrous oxide lost by diffusion into the patient; (iv) nitrogen gained by the circuit by diffusion from the patient.

The patient therefore breathes a complex mixture, but there is in common use a general formula to estimate the oxygen percentage being inhaled. The original publishers (Foldes *et alii*) stated that there was a greater discrepancy in their calculations, the smaller the total flow used and the longer the duration of the anæsthetic. This dis-

TABLE I.

Actual and Calculated Oxygen Percentages in Delivered Gas for Various Gas Mixtures and Different Boyle's Machines.

Gas Mixture.[1]	Oxygen Percentage in Delivered Gas.									
	Actual.									Calculated.
	Machine A.	Machine B.	Machine C.	Machine D.	Machine E.	Machine F.	Machine G.	Machine H.	Machine I.	
5 : 2	31	29	30	30	26	26	30	30	30	28
2 : 1	35	34	35	35	33	31	36	34	37	33
1 : 1	53	50	50	52	50	46	54	48	54	50
1 : 0·5	40	34	34	37	35	33	38	36	40	33

[1] Gas mixture denotes flows of nitrous oxide and oxygen in litres per minute.

crepancy was reduced if the patient's basal consumption of oxygen was added to the original flows calculated to produce the desired concentration of oxygen. Eventually, it was found that 15% more than the calculated basal requirement had to be added.

Shackman *et alii*, using a thiopentone-nitrous-oxide-curare sequence, and premedicating with morphine and atropine or "Omnopon" and scopolamine, found that, in a great proportion of their cases, there was a reduction in basal oxygen consumption, but that in some there was in fact an increase.

TABLE II.

Dental Anæsthetic Machines.

Table IIA.

Actual and Indicated Oxygen Percentages in Gas Delivered from Machine "W" at Various Pressures.

Reading on Oxygen Percentage Dial.	Actual Oxygen Percentage of Gas Delivered.				
	Position 1.[1]	Position 2.[1]	Position 4.[1]	Position 6.[1]	Position 8.[1]
5	No flow.	5	5	5	4
10	No flow.	11	14	8	8
15	No flow.	17	13	10–15	14
20	No flow.	18–20	18–20	34–38	31
50	No flow.	34	62–94	84	80

[1] Reading on pressure indicator dial.

Table IIB.

Actual and Indicated Oxygen Percentages in Gas Delivered from Machine "M" at Various Pressures.

(Reducing valves at 60 lb. per square inch were attached to this machine.)

Reading on Oxygen Percentage Dial.	Actual Oxygen Percentage of Gas Delivered.			
	5 mm.[1]	10 mm.[1]	20 mm.[1]	30 mm.[1]
10	8	8	8–6	7
15	13–14	13	12	12
20	19–20	20	19–18	20
50	43	42	42	42

[1] Indicated pressures in millimetres of mercury.

Topkins and Artusio have shown recently that, with ether and cyclopropane, there was an average increase in basal oxygen consumption of 9% and 15% respectively.

In confirmation of this, Petersen and Elam have shown that, with the combined use of thiopentone, morphine and nitrous oxide, there was a decrease in carbon dioxide output, but there was a significant and constant increase in carbon dioxide output where ether was used, despite increases in the alveolar concentration of carbon dioxide.

The formula in common use is as follows:

$$\text{Oxygen percentage} = \frac{A - B}{(A - B) + C} \times 100$$

where A is oxygen flow, B is oxygen consumption, and C is nitrous oxide flow, all in millilitres per minute.

Foldes estimated oxygen consumption on a weight basis as follows: a body of 100 lb. requires 200 ml. per minute; a body of 100 to 150 lb. requires 250 ml. per minute; a body of more than 200 lb. requires 350 ml. per minute. The range of oxygen consumption that may be found in practice is, of course, extremely wide, but Foldes, by estimating basal oxygen consumption on a weight basis and by periodically emptying the reservoir bag, could maintain the oxygen delivered to within 5% of the calculated figure.

Shackman and Graber found in their series that, during anæsthesia, the range was 120 to 212 ml. per minute; and Topkins and Artusio's range was 176 to 299 ml. per minute for cyclopropane, and 120 to 305 ml. per minute for ether.

By means of the oxygen analyser, a series of cases was investigated (Table IV) in which different flows were being utilized. The frequency of the recordings bears no relation to the frequency of use of such flows as, indeed, some flows recorded were employed for purposes of investigation only. However, it is known that such flows are currently being used. Some anæsthetists have altered their oxygen flowmeters so that 750 ml. of oxygen can be measured. Readings from one such machine have been included in the group in which the flows were 700 ml. of oxygen. In most anæsthetic machines available, it is impossible accurately to measure a flow of 750 ml. of oxygen.

The range of figures represent readings taken from the distal end of the corrugated tube or the Magill tube at inspiration.

In the calculation of the oxygen percentage inhaled, a consumption of 300 ml. per minute was assumed. It is apparent from the recordings made that, even when allowance is made for the greatest estimated consumption, and also for the fact that most anæsthetic machines favoured with an excess of oxygen, the inhaled oxygen may be below the calculated figure.

It should be noted that, of the mixtures known to be in current use, the most deceptive and most likely to produce hypoxia is that of the so-called 2:1 mixture of 500 ml. of oxygen and 1 litre of nitrous oxide per minute, although the delivered oxygen content would be 33%. Results of one prolonged investigation of such a mixture are reproduced (Figure IV) to show that, even with controlled respiration, the oxygen content continually falls. It should also be noted that changing the gases in the bag raises the oxygen atmosphere only temporarily.

It is in this type of circuit that minimal flows are used. Woolmer, in an attempt to use nitrous oxide in a closed circuit with a total flow of gases of 400 to 450 ml. per minute, by continual monitoring of the circuit gases by means of an oxygen analyser, could only maintain the oxygen concentration at 22% to 24%.

Optimum Content of Oxygen.

Whatever the concentration of oxygen delivered to the patient, the actual concentration reaching the alveoli and so absorbed will be less. This obtains in the normal physiological state; if the inhaled percentage is 20% oxygen, the alveolar content is 14%. Similarly, in anæs-

thetic practice in a semi-closed circuit administering 80% nitrous oxide and 20% oxygen, the alveolar concentration will be 80% and 10% respectively, when there is no extended dead space. This occurs with nitrous oxide given intranasally when each exhalation is expended and each inhalation is made with fresh gases. With such a system and with percentages delivered as mentioned, there is no marked disturbance of arterial blood oxygen concentration. With further reduction to an inhaled oxygen mixture of 19%, desaturation of the hæmoglobin commences, and at an oxygen inhalation of 18% (which gives an arterial oxygen saturation of 94%), the physiological reaction to anoxia can be observed.

TABLE III.

Effect of Ambient Temperature on Vaporization of Ether and Hence the Oxygen Percentage of Gas Delivered by Boyle's Bottle.

Minutes from Commencement.	Oxygen Percentage of Gas. At 23° C.[1]	Oxygen Percentage of Gas. At 21° C.[2]	Method of Supplying Gases.
0	29	72	Through ether
1		64	
2	27		
3		68	
5	27		
10	27	68	
15	27	70	
20	28	70	Over ether
25	27	71	
30	27		
35		71	

[1] Nitrous oxide and oxygen were supplied at the rate of 5 and 2 litres per minute respectively.

[2] Nitrous oxide and oxygen were supplied at the rate of 2 and 5 litres per minute respectively.

TABLE IV.

Calculated and Actual Oxygen Percentages of Gas Delivered in Closed Circuit with Spill.

Flow of Gas in Litres per Minute (Oxygen : Nitrous Oxide).	Calculated Oxygen Percentage in Fresh Flow.	Calculated Oxygen Percentage Inhaled.	Actual Oxygen Percentage of Samples Taken. (Range.)	Number of Cases.
1 : 2	33	29	28–30	6
1 : 3	25	21	20–23	5
0·7 : 1 (0·75 : 1)	41	29 (31)	30–36	4
0·7 : 2	26	17	19–26	7
0·5 : 1	33	17	19–24	3
2 : 2 and halothane 1·5%	48·5	46	43–54	5

One could, of course, go to the other extreme and use a very high concentration of oxygen. This is common practice with the more potent agents such as cyclopropane, ether and halothane. With halothane, for example, when denitrogenation has been performed, after 30 minutes of anæsthesia and a flow of 500 ml. of oxygen per minute, it is common to find an oxygen content of 90%. When no such denitrogenation has occurred, a 58% mixture has been found. However, there are several stated disadvantages with such a high oxygen atmosphere, although it is in fact commonly used. Briefly, some of the disadvantages are as follows: (i) it masks the presence of carbon dioxide; (ii) it leads to excessive carbon dioxide build-up in the tissues; (iii) it renders some mixtures explosive; (iv) it predisposes to atelectasis of the lungs; (v) it cannot be used with nitrous oxide unless some potent supplementary agent is given.

On the other hand, it is well known that deficiency of oxygen, and not necessarily an anoxic mixture, produces irreparable cerebral damage or cardiac arrest. What is not realized is that the classical signs of hypoxia—cyanosis, loss of consciousness, tachycardia and hyperventilation—may be masked during an anæsthetic procedure, and the first evidence of such hypoxia may be a catastrophic event.

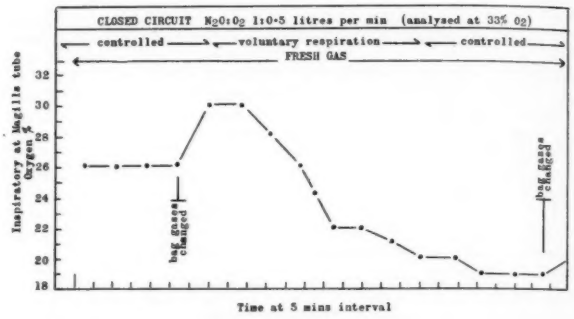


FIGURE IV.

Graph showing results of an investigation of a so-called 2 : 1 mixture of oxygen and nitrous oxide, delivered in closed circuit (1 litre nitrous oxide and 0·5 litre oxygen per minute) and supposed to produce an oxygen atmosphere of 33%. The oxygen content of the inspired air in the Magill tube is measured at five-minute intervals and is shown to fall during controlled respiration. Changing the gases in the bag raises the oxygen atmosphere only temporarily.

Cyanosis.

Under certain conditions existing during anæsthesia, cyanosis may be impossible to detect. Further, the degree of cyanosis depends upon so many variables in the patient, and the detection depends upon the acuity and the experience of the observer. All investigators agree that it is not a constantly reliable sign of hypoxia.

Weitzner *et alii*, inflating the patient's lungs with air for two minutes, showed that a period of one minute of apnœa lowered the oxygen saturation to 88%, and in the next 30 seconds of apnœa the oxygen saturation fell to the dangerous level of 55% to 45%. Further, cyanosis was evident in only one subject, and this at an oxygen saturation of 48%, although there were three observers looking specifically for this sign.

Comroe and Botelho also believe that the presence and degree of arterial oxygen saturation are difficult to assess clinically. In their series, 96 observers were unable to detect cyanosis until saturation was 80%. Thirty-one of the observers could not detect cyanosis with certainty until the oxygen saturation fell to 71%.

Tachycardia.

The pulse rate under anæsthesia is influenced by many factors, some producing tachycardia, some bradycardia.

Dripps and Comroe (quoted by Comroe and Botelho) found that, in the conscious, unpremedicated patient, an increase in the pulse rate was not marked, requiring a 12% oxygen inhaled mixture to produce a 16% increase in pulse rate. This would mean, for a normal pulse rate of 80 per minute, the increase would produce a pulse rate of only 92 per minute.

Unconsciousness.

Unconsciousness, of course, cannot be determined in the anæsthetized subject, but hypoxia may prevent the return of consciousness. It is maintained that, with the induction of anæsthesia with 100% nitrous oxide, it is the anoxia which produces unconsciousness. At 85% arterial oxygen

saturation, there is disturbance of higher cortical activity and special senses. Unconsciousness is complete when the venous blood leaving the brain has an oxygen tension of 24 mm. of mercury.

Hyperventilation.

Hyperventilation in the anæsthetized patient, and especially when the patient's respiratory musculature is paralysed with relaxing agents, can rarely be used as a sign of hypoxia. Below a concentration of 12% of oxygen in the inspired atmosphere, pulmonary ventilation can be seen to be considerably increased in the conscious patient. This hyperventilation can be observed with nitrous oxide induction when oxygen is restricted. It occurs through stimulation of the chemoreceptors and commences when the inhaled oxygen concentration is lower than 18%. Hypoxia actually depresses the cells of the respiratory centre and anoxia destroys them. The hyperventilation which occurs is apparently a primitive and protective type of respiration.

Comment.

The foregoing signs then of hypoxia may thus be masked during an anæsthetic procedure. Nevertheless, they are all closely watched for, their presence probably indicating that hypoxia is already marked.

The disadvantages of both high and low oxygen atmospheres have been detailed. There is usually no problem when potent anæsthetic agents are employed, provided that, when such high concentrations of oxygen are used, adequate ventilation is maintained at all times to prevent hypercarbia. The problem is most marked when nitrous oxide is employed in closed circuits. Nitrous oxide is a weak agent, and, for it to be successful, a continuous and high alveolar concentration of it must be maintained. The effect of nitrous oxide is diminished if nitrogen is allowed to remain, or if high oxygen atmospheres are used. It is also reduced if the volume of nitrous oxide supplied is less than that taken up by the body, or lost by spill and leakage, and including that lost in blood loss. Although a satisfactory brain concentration is reached within 10 minutes to produce anæsthesia when an 80% mixture of nitrous oxide is inhaled, the body does not become saturated for hours. Consequently, even in a closed circuit, nitrous oxide must be continuously supplied and a high oxygen content cannot be used concurrently.

It has been shown that, under optimum conditions, the error in estimating the oxygen content in the inspired mixture can be 5% or more. It has also been shown that the adequate ventilation of apnœic patients with air (20% oxygen) does not produce physiological saturation of the hæmoglobin, and not more than one minute of apnœa can be allowed. The inhalation of an 80%-20% nitrous oxide mixture (producing an alveolar content of 10% oxygen) does not materially alter the oxygen saturation, provided that no rebreathing occurs.

Faulconer and Latrell have shown that, with prolonged periods of anæsthesia, there is a decrease in oxygen saturation without there being any depression of oxygen tension in the mixture below the mask, and the decrease is not always associated with inadequate respiration. This has been clarified by Campbell *et alii*, who have shown that an increase of 5% above the physiological 5% right-to-left shunt occurs in anæsthetized persons breathing spontaneously. There appears to be a disturbance of the normal relationship between the pulmonary blood flow and the pulmonary ventilation (Read) resulting in only 90% saturation of the hæmoglobin.

It would appear therefore that, in an anæsthetized subject, an atmosphere of not less than 20% oxygen should be utilized if there is no rebreathing, and an atmosphere of not less than 25% oxygen if there is to be rebreathing. For the ill, and in special circumstances in which there may be a disturbance of pulmonary or cardio-vascular physiology, a much higher oxygen atmosphere must be supplied with probably higher rates of alveolar ventilation.

Other Causes of Hypoxia.

Churchill-Davidson and Wylie state that the simplest cause of anoxia is a failure to administer a sufficient percentage of oxygen in the inspired air (mixture). The factors involved in this have been outlined above. To this statement must be added that the most common cause of hypoxia is inadequate pulmonary ventilation. Even with a lowered inspired oxygen concentration and adequate pulmonary ventilation, it is possible, at least for a time, to maintain adequate oxygenation by the opening up of more alveoli. This is obvious in mouth-to-mouth resuscitation, and, in the Ikezomo series already quoted, where air was used as the diluent in ether anæsthesia. During anæsthesia, adequate pulmonary ventilation with an adequate supply of oxygen maintains oxygen saturation at least 90%.

To elaborate on the most common causes of inadequate ventilation is not the purpose of this paper and it would be reiterating something that is continually being discussed and written about, but rarely corrected. Obstruction of the upper respiratory airway, and allowing patients whose respiratory centres have been depressed with premedication and anæsthetic agents, or whose respiratory musculature has been paralysed with relaxing agents, to breathe spontaneously, still remain the commonest causes of inadequate ventilation.

Summary.

The causes of inadequate oxygen concentrations in anæsthetic mixtures have been detailed.

When there is any doubt as to the concentration of the inspired oxygen, the anæsthetist must provide an obvious excess, as it has been shown that hypoxia may be difficult to detect clinically.

The means of providing adequate oxygenation of the alveoli and the minimal inspired concentration have been defined.

The literature on the subject has been reviewed. Some personal investigations have been recorded in an attempt to clarify some of the problems involved, and to show what concentrations of oxygen may be found in the various anæsthetic circuits in common use.

The writer is aware, of course, that the partial pressure of oxygen in the alveolar mixture is one of the main factors in determining the rate of absorption of this gas; but percentages have been used in this paper so that the common causes of hypoxia might be the more easily understood. Further, in anæsthetic practice, improvement of oxygenation is produced by an increase in the content of oxygen in the inspired mixture, and by the maintenance of adequate ventilation, so that more alveoli are functioning to absorb the gas.

The principles described herein form some basic principles in the practice of anæsthesia; in view of the findings of the research reported here, and another investigation proceeding, no excuse is needed for their reiteration.

References.

ADRIANI, J. (1959), "Fundamentals of General Anæsthesia for Dentistry", Blackwell, Oxford.

AYRE, P. (1956), "The T Piece Technique", *Brit. J. Anæsth.*, 28: 512.

BOURNE, J. G. (1960), "Nitrous Oxide in Dentistry", Lloyd-Luke, London.

CAMPBELL, E. J. M., NUNN, J. F., and PECKETT, B. W. (1958), "Comparison of Artificial Ventilation and Spontaneous Ventilation with Reference to Ventilation-Blood Flow", *Brit. J. Anæsth.*, 30: 166.

CHURCHILL-DAVIDSON, M. C., and WYLIE, W. P. (1960), "Anæsthetic Practice", Lloyd-Luke, London.

COMROE, J. H., and BOTHELO, S. (1947), "The Unreliability of Cyanosis in the Recognition of Arterial Anoxemia", *Amer. J. med. Sci.*, 214: 1.

DRIPPS, R. D., and COMROE, J. H. (1947), quoted by Comroe and Botelho, *Amer. J. med. Sci.*, 214: 1.

EVANS, F. T., and GRAY, C. T. (1959), "General Anæsthesia", Butterworth, London.

FAULCONER, A., and LATRELL, K. E. (1949), "Air-Ether Method of Anesthesia", *Anesthesiology*, 10: 247.

FITTON, E. P. (1958), "Theoretical Investigations of Oxygen Concentration in Gases Inspired from Various Semiclosed Anæsthetic Systems", *Brit. J. Anæsth.*, 30: 269.

FOLDES, F. F., CERAVULO, A. J., and CARPENTER, S. L. (1952), "Nitrous Oxide-Oxygen Anæsthesia in Closed Systems", *Ann. Surg.*, 136: 978.

GUSTERSON, F. R., and CLARK, J. M. (1960), "The Use of the Goldman Halothane Vaporiser in the Closed Circuit", *Brit. J. Anæsth.*, 32: 388.

HALL, J. E. (1955), "Physiology of Respiration in Infants and Young Children", *Proc. roy. Soc. Med.*, 48: 761.

HARRISON, G. G., and JONES, C. S. (1955), "Carbon Dioxide Concentration in the Boyle's Type Anæsthetic Machine", *Brit. J. Anæsth.*, 27: 162.

HUNTER, J. D. (1958), "A New Gas Oxygen Dental Anæsthetic Machine", *Brit. J. Anæsth.*, 31: 367.

IKEZOMO, F., HARMEL, M. H., and KING, B. D. (1959), "Pulmonary Ventilation and Arterial Oxygen during Ether-Air Anesthesia", *Anesthesiology*, 20: 597.

INKSTER, J. S. (1956), "The T Piece Technique in Anæsthesia", *Brit. J. Anæsth.*, 28: 512.

JACKSON REES, G. (1960), "Pædiatric Anæsthesia", *Brit. J. Anæsth.*, 32: 132.

MACINTOSH, R. R., and MUSHIN, W. W. (1946), "Physics for the Anæsthetist", Blackwell, Oxford.

MAPLESON, W. W. (1954), "The Elimination of Rebreathing in Various Semiclosed Anæsthetic Systems", *Brit. J. Anæsth.*, 26: 323.

MAPLESON, W. W. (1957), "Trichlorethylene Concentration from a Boyle Type Anæsthetic Apparatus", *Brit. J. Anæsth.*, 29: 3.

MICKLEM, N. J., and JONES, C. S. (1957), "Partial Pressure of Oxygen in the Magill Attachment", *Brit. J. Anæsth.*, 29: 491.

PETERSEN, P. N., and ELAM, J. O. (1958), "The Elimination of Carbon Dioxide", *Anesth. et Analg.*, 37: 91.

READ, J. (1961), "Respiratory Insufficiency", MED. J. AUST., 1: 83.

RUBIN, H. M. (1953), "Concentration of Inhaled Gas", *Anesthesiology*, 14: 457.

SHACKMAN, R., GRABER, B., and REDWOOD, C. (1951), "Oxygen Consumption and Anæsthesia", *Clin. Sci.*, 10: 219.

SWARTZ, C. H., ADRIANI, J., and MIH, A. (1953), "Semiclosed Inhalers: Studies of Oxygen and Carbon Dioxide Tension", *Anesthesiology*, 14: 437.

SYKES, M. K. (1959), "Rebreathing during Controlled Respiration with the Magill Attachment", *Brit. J. Anæsth.*, 31: 247.

TOPKINS, M. J., and ARTUSIO, J. F. (1956), "The Effects of Cyclopropane and Ether on Oxygen Consumption in the Unpremedicated Patient", *Curr. Res. Anesth.*, 35: 350.

WEITZNER, S. W., KING, B. D., and IKEZOMO, E. (1959), "The Rate of Arterial Oxygen Desaturation", *Anesthesiology*, 20: 624.

ON THE MALIGNANT VARIETY OF CYSTOSARCOMA PHYLLODES OF THE MAMMARY GLAND.

By G. S. SANTOW, M.D. (Budapest), Dip.Surg. (Budapest), *Sydney*.

IN the title of this paper the malignant properties of cystosarcoma phyllodes, which has the word "sarcoma" incorporated in its name, are stressed. It is thus implied that this diagnosis of cystosarcoma phyllodes does not in itself indicate clinical malignancy. Moreover, as far back as 1838, Johannes Mueller described cystosarcoma phyllodes as "a perfectly innocent disease, as far removed from carcinomas as are those non-suppurating condylomas of the penis that have more than once been mistaken for cancerous structures". Practically every author has stressed the innocence of these tumours, although a certain number of such tumours have recurred locally after incomplete local excision has been carried out as the sole treatment. McDonald and Harrington have collected a score of names by which these same tumours are denoted. The vast majority of these tumours, probably about 90%, are benign, and only about 1 in 10 are malignant. Geschickter sums it up pointedly by saying that the total number of sarcomas of the breast is small, but the number of pathological types is great. The mesenchymal elements in the mammary gland have not the susceptibility to malignant changes that the epithelial elements of the breast possess. If this was not so, the ratio of sarcoma to carcinoma in the breast would be quite a different one. Sarcomas originating in the fibrous stroma of the gland may grow to immense size, and as a rule metastasize relatively late. These sarcomas are of two forms: (i) mammary fibrosarcoma, which is primary to the connective tissue; (ii) primary adenosarcomas, arising out of fibroadenomas, containing a few epithelial elements. Approximately half of all mammary sarcomas belong to these two varieties, whilst the other half are called by Geschickter non-indigenous sarcomas. These latter contain vascular structures, fat and nerve sheath and are mixed tumours. Wellbrook reported 29 sarcomas out of a series of 7763 mammary lesions. In the literature the ratio has been variously estimated as one sarcoma to 100 carcinomas and one sarcoma to 300 carcinomas. The ratio in the recent literature tends to be rather less, as the cystosarcomas and the giant intracanalicular myxomas are being excluded. Lee and Pack summarized the literature in 1931, and found 109 cases of cystosarcoma phyllodes described. To this number they have added four cases of their own. Salient clinical features included the following.

1. There is a "precursory" tumour present in the breast, which remains more or less unaltered over a period of many years. Cases are known in which such a tumour has been observed by the patient for as long as nine years without any change in size. However, these original tumours, which are, of course, fibroadenomas, may undergo some change and start a period of rapid growth. It is known that within six months such tumours have grown as much as approximately 6 lb. in weight.

2. Lactation has a stimulating effect on these tumours. Schoenherr (1960) recently surveyed the literature on the relationship between breast tumours and hormonal influences in pregnancy and lactation.

3. In one-quarter of these tumours an ulcerated lesion is present owing to break-through of the rapidly growing mass.

4. The two significant features obvious at first inspection are, first, the large size, and secondly, the fact that most of the breast is involved.

5. Often malignant change is reported.

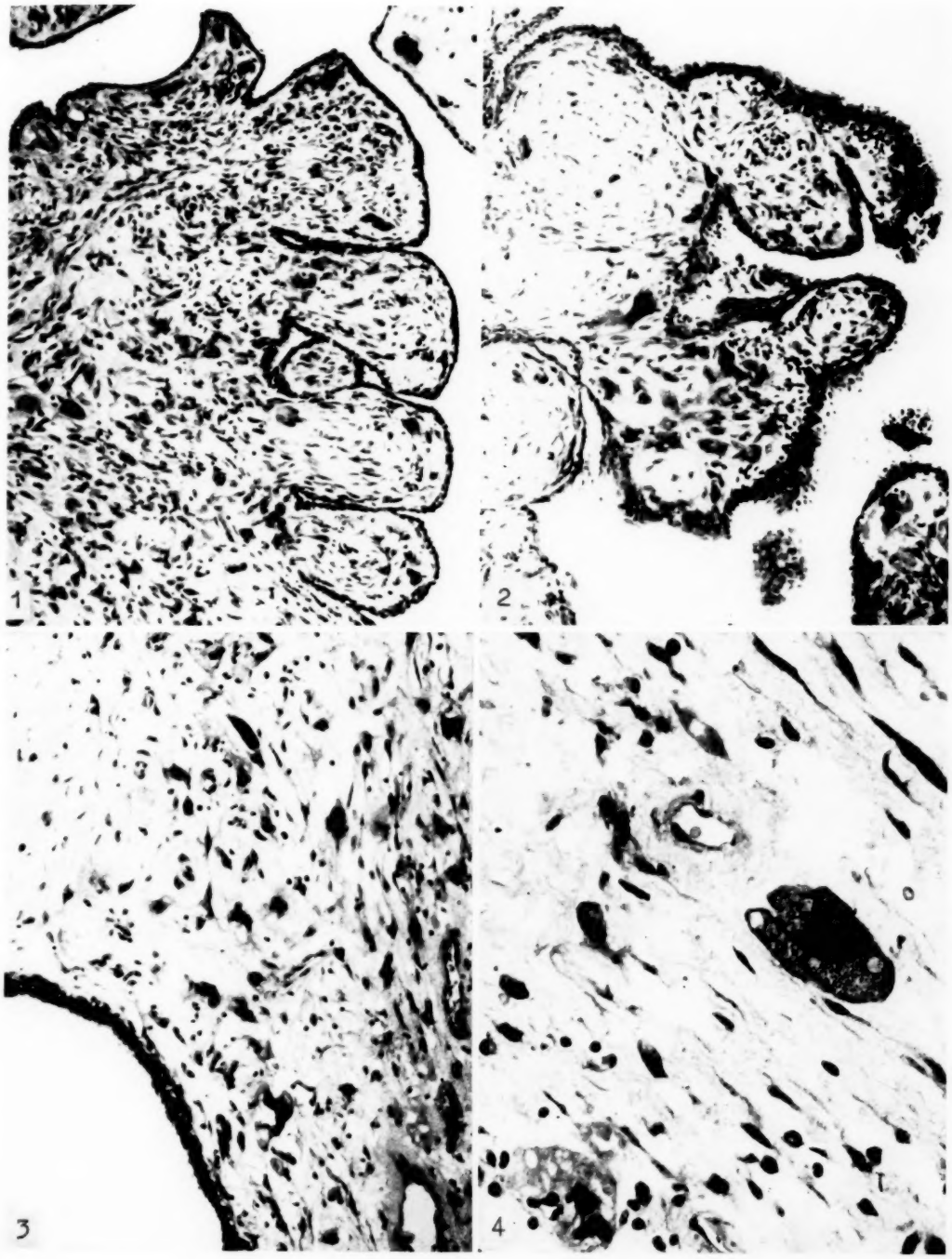
6. Many of the giant fibroadenomas have appeared in adolescent girls.

In the material of the Mayo Clinic from 1904 to 1943, 13 cases of giant fibroadenomas were found. Of these cases, in two malignant change occurred. Whilst in ordinary fibroadenomas the incidence of bilaterality was 6%, in the giant tumours in one-third of the cases both breasts were involved. The pathological characteristics were as follows. Macroscopically, diffuseness, finger-like projections and cyst formation were observed. Microscopic examination revealed fibroadenomatous features (pericanalicular and intracanalicular), myxomatous stroma and also hyalinization, acini lined with a single layer, and necrosis in some areas. The size of the tumour alone is not in itself proof of malignancy. Cystosarcoma phyllodes or giant fibroadenoma is a potentially malignant tumour.

Cooper and Ackerman published three cases of cystosarcoma phyllodes showing a variety of speed in growth. Two cases gave evidence of fast growth after years of quiescence; but the tumours did not recur after local excision. In one case the tumour recurred three times after local operation, and the patient died from metastases. White's case was quiescent for two years. On the basis of a preexistent fibroadenoma, a tumour of extensive proportions arose. The small tumour, first discovered as a fibroadenoma, was excised after a period of rapid growth had taken place. Examination of the tumour showed mucoid degeneration, cavity formation and malignant changes of a sarcomatous nature, and the tumour recurred twice after excision. The patient died a short while after from secondary deposits.

According to impressions obtained from the cases published, cystosarcoma phyllodes and its malignant varieties are radio-resistant tumours. In many cases local excision only was the extent of surgical treatment. It seems to me that simple mastectomy with removal of

ILLUSTRATIONS TO THE ARTICLE BY G. S. SANTOW.



ILLUSTRATIONS TO THE ARTICLE BY N. R. NOBLE.

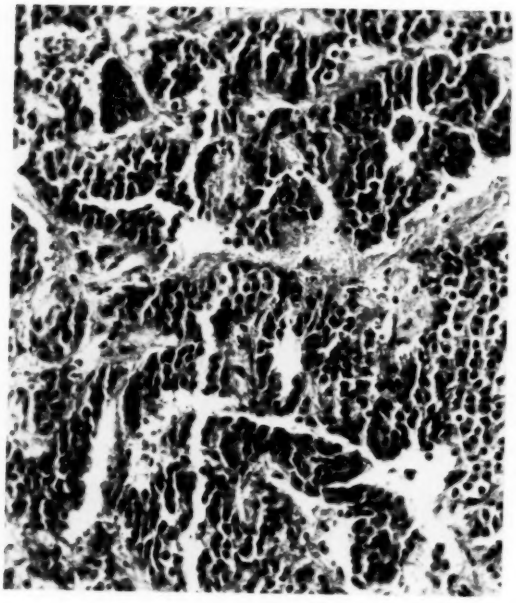


FIGURE I.

Argentaffin carcinoma showing clumps of small cells in alveolar formation. (Hæmatoxylin and eosin, × 240.)

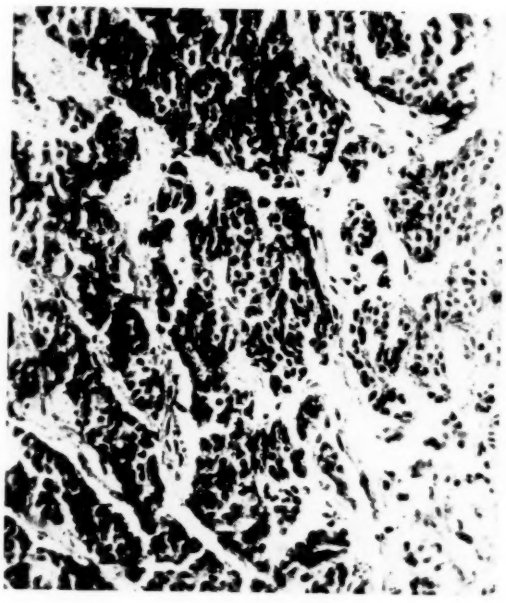


FIGURE II.

Gomori's methenamine silver reduction reaction showing silver-stained granules in the tumour. × 100.

FIGURE III.

Terminal portion of the ileum, showing on the extreme left a polypoid filling defect in profile.

FIGURE IV.

Later film with compression (the caecum is now filled), showing several rounded filling defects *en face*.

the pectoralis fascia is the treatment of choice. Apart from a few very advanced cases, the disease does not progress into the lymph glands and extension to the axilla is not observed. Hence radical mastectomy is not recommended for this condition.

Report of a Case.

A single girl, aged 17 years, presented herself with a lump in the outer upper quadrant of her right breast. This lump, which was freely movable, measured approximately 5 cm. in diameter; the skin over it looked intact. This lump was removed for histological examination, and when cut across it was found to contain a cyst with a wall of firm white tissue and a smooth lining. Also it contained a yellowish papillary mass, approximately 3 cm. in diameter. The cyst wall was hyaline fibrous tissue, in which there were mildly dilated cystic ducts and a little glandular tissue. The lining was flat epithelium, and the cyst was regarded as a duct grossly dilated by the papilloma which it was seen to contain (Figure I[1]). This tumour was regarded as belonging to the type described as cystosarcoma phyllodes. It had features typical of sarcoma (Figure II). Malignant changes had occurred in the stroma; nuclear pleomorphism and multinucleate tumour cells were prominent, and abnormal mitoses were present (Figures III and IV).

Surgical treatment, consisting of simple mastectomy and removal of the pectoral fascia, was performed. Dissection of the mastectomy specimen showed dense fibrosis extending through most of the breast. The fibrosis was bounded on the deep plane by pectoral fascia and on its medial upper lateral and caudal margins by adipose tissue. Tissue for preparation of sections was selected from the sites named and from the sites of the original biopsy specimen also. Microscopic examination of all those sites showed dense interstitial fibrosis, but lobular hyperplasia was not found. Some ducts were slightly dilated, but there was no hyperplasia of the epithelium. No residuum of the tumour was found. The patient was reexamined 15 months after the operation, but no recurrence was found. She remains in good health.

Summary.

1. Cystosarcoma phyllodes of the mammary gland is usually thought of as a non-malignant growth. Malignant varieties of this tumour are known to occur on a basis of benign fibroadenomas, which have been present for many years in a quiescent state preceding a state of fairly rapid growth.

2. The result of malignant changes corresponds histologically to an adenosarcoma.

3. In the present case, a single girl, aged 17 years, presented herself with a small movable, painless, hard lump, 5 cm. in diameter, the existence of which had been known to the patient only for a short time.

4. Cystosarcoma phyllodes may occur in a malignant form even though the lump is still quite a small one. The treatment of choice is simple mastectomy.

Acknowledgement.

I am grateful to Dr. G. V. Rudd, who carried out the pathological examination.

References.

COOPER, W. G., and ACKERMAN, L. V. (1943), "Cystosarcoma Phyllodes with a Consideration of its More Malignant Variant", *Surg. Gynec. Obstet.*, 77: 279.

GESCHICKTER, C. F. (1945), "Diseases of the Breast", Lippincott, London.

HILL, R. P., and STOUT, A. P. (1942), "Sarcoma of the Breast", *Arch. Surg.*, 44: 723.

MCDONALD, J. R., and HARRINGTON, S. W. (1950), "Giant Fibro-Adenoma of the Breast—Cystosarcoma Phyllodes", *Ann. Surg.*, 131: 243.

ROSS, D. E. (1952), "Cystosarcoma Phyllodes", *Amer. J. Surg.*, 84: 243.

ROSS, D. E. (1954), "Malignancy Occurring in Cystosarcoma Phyllodes", *Amer. J. Surg.*, 88: 243.

SCHOTTENFELD, L. E. (1954), "Sarcoma of Breast; Review of Literature with Report of 14 Cases", *Amer. J. Surg.*, 88: 243.

SCHOENHERR, W. (1960), "*Sarcoma der Brust und Schwangerschaft*", *Z. Geburtsh. Gynäk.*, 154: 270.

WHITE, J. W. (1940), "Malignant Variety of Cystosarcoma Phyllodes", *Amer. J. Cancer*, 40: 458.

[1] For Figures I to IV see art-paper supplement.

Legends to Illustrations.

FIGURE I.—Papilloma with finger-like projections.

FIGURE II.—Sarcomatous changes present in the stroma of papilloma.

FIGURE III.—Malignant changes in the stroma: pleomorphism and multinucleated tumour cells.

FIGURE IV.—Giant cells in the stroma showing sarcomatous changes.

Reports of Cases.

A CASE OF CARCINOID SYNDROME, WITH AN ACCOUNT OF THE USE OF ALPHA-METHYL-DOPA.

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THE production of a characteristic group of symptoms by malignant carcinoid has been well documented by overseas workers. The following is the report of a case seen recently in the Repatriation General Hospital, Concord.

Clinical Record.

The man, aged 47 years, first presented at the hospital in October, 1960. He had a long history of mild asthma dating from 1943. In 1953, he made application for life assurance, but was rejected because he was found to have aortic stenosis. He has not been troubled by this latter disability. For fifteen months he had complained of intermittent flushing attacks, which lasted four or five minutes and involved his face and the upper part of his chest. They would be precipitated by emotional stimuli and were sometimes associated with asthma attacks. Since March, 1960, these attacks had become more pronounced. He next noticed intermittent diarrhœa. The attack would last one day, during which he would pass about 20 fluid motions which never contained any blood or mucus. His bowel motions would be normal between attacks. About June, 1960, he noticed increasing shortness of breath on exertion and some slight ankle œdema. Six weeks later he noticed a swelling in his right hypochondrium and complained of a dragging sensation there. During his illness he had not lost any weight, and he had felt well otherwise.

On examination, the patient was well nourished. He was noted to have a florid facies with some associated telangiectasia. His jugular venous pressure was raised, and prominent "a" and "v" waves were seen. There was some pitting œdema of his ankles. Grade II aortic ejection type systolic and Grade I early diastolic aortic murmurs were heard. A Grade I tricuspid diastolic murmur was heard also by the visiting cardiologist. No tricuspid systolic murmur was heard. No increase in his blood pressure was noted during an attack of flushing. The murmur heard in the aortic area was considered to be a transmitted one from the pulmonary valve stenosis. Generalized expiratory wheezing was present in the chest on auscultation. The liver was enlarged to four fingers' breadth below the costal margin, and was smooth and non-tender. A large, smooth, non-tender mass three inches in diameter was present in the left lobe. There were no pellagra-like skin lesions, and no abnormalities were detected in his fundi.

The following investigations were performed. On several occasions his urine was noted to be almost red on standing. There was no microscopically evident hæmaturia (or porphyrinuria). The 24-hour excretion of histamine was greatly increased. The excretion of 5-hydroxy-indole-acetic

acid (5 HIAA) over 24 hours varied between 320 and 600 mg. Five-hydroxytryptamine (5 HT) excretion over 24 hours varied from 0·46 to 3·68 mg. per day (normal, 0·1 mg. per day). His blood count was normal. Liver function tests revealed no hypoproteinæmia, and the only abnormal findings were a serum alkaline phosphatase level of 16·6 King-Armstrong units and a "Bromsulphalein" retention of 51%. The S.G.O.T. estimation was 8 units. The serum electrolytes were normal. An electrocardiogram showed non-specific *RS-T* segment changes with large *U* waves. A chest X-ray film showed some left ventricular enlargement. A barium-enema X-ray examination was done by Dr. J. Colclough, and part of the terminal part of the ileum was outlined and multiple small filling defects were demonstrated. A barium-meal and follow-through X-ray examination showed further small filling defects in the ileum, but no evidence of peptic ulceration, intestinal obstruction or hurry was noted. A biopsy of the mass in his liver was done. The section showed infiltration of the liver by tumour consisting of well-defined solid clumps of small polyhedral cells, and was said to be diagnostic of carcinoid tumour. The silver-staining granules were demonstrated also.[1]

Cardiac catheterization studies showed a low cardiac output of 2·47 litres per minute and pulmonary valve stenosis. There was gross tricuspid valve incompetence with some stenosis. The right auricle/right ventricle diastolic gradient ranged from 6 to 10 mm. of mercury. There was low pulmonary vascular resistance, normal arterial oxygen saturation and normal left atrial pressure. There were no hæmodynamic changes six minutes after 50 mg. of iproniazid had been given intravenously.

Discussion.

The first description of carcinoid tumour was given by Merling in 1808 (according to Steger and Avanzini, 1953-1954). Oberndorfer (1907) introduced the term *Karzinoiden*, indicating a malignant appearance but having a benign course. The term "carcinoid" is preferred to argentaffinoma, because affinity for silver is not specific to these cells, especially in lung and rectal carcinoids. The silver-staining granules have been demonstrated to be artefacts, and appear only when the tissue has been preserved in formol saline and not alcohol. The term "carcinoid tumour" is employed without any implication regarding the degree of morphological or clinical malignancy of the tumour.

Various components of the syndrome were described by different workers, but Thorson *et alii* (1954) were the first to integrate these into the carcinoid syndrome. However, Sir Maurice Cassidy in 1931 presented two male patients with recurrent phenomenal flushing of the face and parts of the trunk, with associated carcinoma of the abdominal viscera, notably the liver.

Masson (1928) described three types of cells in carcinoid tumour. The commonest are round or polygonal cells; in other cases, "palisade" cells line cell clumps or acini. Mitoses are difficult to find.

The tumour arises from the Kultschitzky cells in the crypts of Lieberkühn. They can arise from any part of the bowel, but are commonest in the appendix and jejunoileum. Carcinoids occur also in the bronchi (Joseph and Taylor, 1960), in teratomas (Thorson, 1958) and in the rectum. There is usually no evidence of elevated tryptophan metabolism with the last-mentioned tumour.

There is a slight male predominance, and they can occur at any age. The size varies from 0·5 to 5·0 cm. in the submucosa, and they are multiple in 33% of cases. Macroscopically they are hard and yellow, but may be grey, white or hæmorrhagic. The yellow is thought to be due to the high content of lipids or yellow pterins. Metastases occur via the lymphatic and perineural spaces or the bloodstream. Most organs in the body can be affected, the liver being the usual site, and metastases can be very large here. Metastatic deposits may increase in size only very slowly. It is very rare for appendiceal carcinoids to have distant metastases, but local involvement of adjacent lymph nodes has been reported.

Multiple secondary deposits with scleroderma-like changes in the skin have been observed (Reingold and Escovitz, 1960).

The Syndrome.

The carcinoid syndrome comprises a characteristic group of symptoms and signs due to the action of serotonin on various organs. It has been shown that serotonin is the main active product of carcinoid tumours.

The commonest feature is episodic facial flushing lasting several minutes. This is usually accompanied by palpitations and tachycardia. The flush may be brief or prolonged, and initially involves only the face and neck. Later the shoulders and the upper part of the trunk may be involved. Eventually there is permanent facial telangiectasia.

Factors which have been found to precipitate attacks include emotion, spices and food, massaging the tumour or metastases, and alcohol (Snow, Lennard-Jones, Curzon and Stacey, 1955).

Next in frequency is watery diarrhœa. This usually occurs first thing in the morning or after breakfast. Diarrhœa, colicky abdominal pain or borborygmi may precede or follow a flush.

Asthma-like respiratory distress accompanies the flushing and diuresis has been observed to follow the flush. The characteristic cardiac murmurs are regarded as late signs.

Other more uncommon manifestations are pellagra-like skin lesions, ascites and ankle œdema. An increased incidence of peptic ulcer has been reported (MacDonald, 1956). Arthritis with swelling and joint stiffness has been noted. Also, sudden episodes of localized œdema of the hands or face have been reported, but a direct relationship to the disease has not always been established (Resnick and Gray, 1960).

An enlarged liver can occur without metastases.

Lesions in the small bowel may cause acute or subacute obstruction necessitating laparotomy. Appendiceal carcinoid is diagnosed after operation.

Biochemistry-Physiology: Pathogenesis.

It has been known for a long time that the serum contains a vasoconstrictor principle and that it is bound to the platelets. The active principle was extracted from beef serum in 1948 (Rapport, 1948), and from the platelets in 1951 (Reid and Rand, 1952). Erspamer since 1938 has extracted a similar substance from a wide variety of vertebrate and non-vertebrate tissues and this has been shown to be identical with the vasoconstrictor substance "serotonin" (Erspamer and Asero, 1952).

It appears that the free plasma serotonin, and not that bound to the platelets, is the biologically active fraction (Magalini and Stefanini, 1956). This is difficult to estimate, and the values obtained in four consecutive cases of carcinoid disease were found to be between 20 and 60 ng. (1 ng. = 10^{-9} grammes) per millilitre (expressed as the base). These values were considered to be falsely high, as in another case of thrombocytopenia and carcinoid disease the free plasma serotonin level was less than 10 ng. per millilitre (Robertson and Andrews, 1961).

Serotonin metabolism in the syndrome is the same as in a normal person. Tryptophan is converted to 5-hydroxytryptophan (5 HTP) and then to serotinin (5 HT). The end product, 5 HIAA, is excreted in the urine and is formed by the action of the enzyme mono-amine oxidase. This is found in high concentration in the liver, the lung and the tumour tissue itself. The main source of 5 HT in patients with metastases in the liver and elsewhere is thought to be these distant deposits. The remainder comes from the tumour and regional metastases, from 5 HT synthesized by the intestinal mucosa and from dietary tryptophan.

There are certain foods that increase excretion of 5 HIAA in the urine, bananas being the most important. Others are tomatoes, avocado, red plum and crustacea. Insect

[1] For Figures I to IV, showing the X-ray appearances and the histological picture, see art-paper supplement.

venoms have the same effect. The drugs that cause an increase are phenothiazine derivatives, acetanalid and mephenesin carbamate. It has been observed rarely in non-tropical sprue that there is a raised excretion of 5 HIAA (Sjoerdsma, 1959).

The 5 HIAA can be detected in the urine by the method of Sjoerdsma, Weissbach and Udenfriend (1955). The normal excretion is 2 to 8 mg. per day, and a figure of over 30 mg. per day is considered to be diagnostic. The liver can metabolize large amounts of 5 HT, so when flushing occurs there are usually hepatic metastases. Besides excreting a large amount of 5 HT direct into the hepatic circulation, they also interfere with the metabolism of 5 HT. However, when carcinoids in teratomas or bronchi drain straight into the caval system, identical symptoms occur with relatively low urinary levels of 5 HIAA (50 to 100 mg.).

A case has been reported by Jones (1957) of malignant intestinal carcinoid with flushing, but without extensive metastases.

Small intravenous injections of adrenaline and noradrenaline given to patients with the carcinoid syndrome produce typical facial flushes. Under these circumstances, the plasma level of free serotonin rises. However, the increased serotonin level is not considered to be the sole cause of the flushing. Infusions of serotonin at varying rates failed to produce the typical facial flushes of a spontaneous attack. The flushes also differed from those provoked by adrenaline or noradrenaline (Peart, Andrews and Robertson, 1961).

The valvular lesions in the heart are predominantly right-sided. This is thought to be due to the action of monoamine oxidase in the lungs, which protects the left side of the heart. Lesions affecting all four valves have been reported in a patient with a patent foramen ovale (Waldenstrom, 1958; Thorson, 1958). The valvular lesions in carcinoid have a structure different from any other type of valvular change. The myocardial lesions are non-specific, and are thought to be due to altered valve function.

The ætiology is considered to be a direct action of the 5 HT causing a fibroblastic reaction. Secondarily released histamine with the relatively low oxygen and high carbon-dioxide content of the right side of the heart may play a part also. There is pearly-grey fibrosis and sclerosis of the pulmonary and tricuspid valves. The chordæ tendineæ are thickened and retracted. Fibrosis is the characteristic histological finding (MacDonald and Robbins, 1957).

It has been postulated that serotonin releases histamine from normal tissue stores (Pernow and Waldenstrom, 1957). The rôle that serotonin plays in anaphylaxis in man is very uncertain (Sjoerdsma, 1959).

The conversion of tryptophan to serotonin in excess instead of niacin is thought to explain the pellagra-like lesions seen occasionally.

Serotonin causes pulmonary vascular constriction during a flushing episode, but has a variable effect on the systemic blood pressure.

The œdema that is seen in these patients can be due to a number of factors, and is not necessarily a sign of cardiac failure. Hypoalbuminæmia and right-sided heart failure may be the cause. Serotonin also has an anti-diuretic effect causing constriction of the afferent renal arterioles (Smith and Murphy, 1960).

Serotonin participates in the function of the central nervous system, but abnormal mental function or striking emotional disorders in these patients are very rare.

Treatment.

The accepted treatment is removal of the primary growth and metastases when this is feasible. Removal of the primary growth is recommended to prevent local complications, such as perforation and obstruction. Deaths have occurred at operation from intense broncho-constriction when traction was applied to the tumour (Smith and Murphy, 1960).

It was considered that this patient was inoperable owing to the extensive tumour masses seen radiologically and to the rapid appearance of the hepatic mass.

Various anti-serotonin metabolites have been tried in the past, without much success. These have included ergot and reserpine alkaloids, lysergic acid diethylamide, radioactive gold, "Marsilid" and phenylacetic acid. Chlorpromazine has been moderately effective.

Ludwig (1960), using iso-nicotinic acid hydrazide (300 to 400 mg. per day) in cases of carcinoid, noted a 30% drop in the excretion of 5 HIAA. The explanation of this is that pyridoxal phosphate is a coenzyme of the decarboxylase reaction which converts 5 HTP to 5 HT. INH renders the coenzyme less available for its enzymatic functions.

Sjoerdsma, Oates, Zaltzman and Udenfriend (1960) have reported their experience in two cases with alpha-methyl-dopa. This blocks the conversion of 5 HTP to 5 HT, causing a rise of 5 HTP excretion in the urine. Its main side effects were mild sedation and hypotension. The drug was given over four to six weeks in a dosage of 5 to 6 grammes per day. It caused a subjective improvement and a drop of 60% to 70% in 5 HIAA excretion.

Initially we gave this patient "Cryptoheptadine" in a dosage of 5 mg. per day with subjective improvement, but there was no change in his 5 HIAA excretion. This drug is an anti-serotonin agent produced by Merck Sharp and Dohme. The patient was digitalized and given diuretics with a good response. He was commenced on "Aldomet" (Merck Sharp and Dohme, alpha-methyl-dopa) and the dosage was gradually increased to 3 grammes per day. Owing to pronounced sedation, he was unable to tolerate larger doses than this. Subjectively he has improved, and the flushing and diarrhœa are less severe. The dyspnœa is unaltered, but the ankle swelling is less. His cardiac murmurs are harsher and his liver has enlarged. There has been no marked reduction in 5 HIAA excretion with this dosage of the drug, and the serotonin precursor, 5 HTP, was not detected in the urine. Since his discharge from hospital, he has continued his profession as a journalist.

The other measures available are the exhibition of additional niacin and the correction of the electrolyte and protein deficiencies that may occur. Paregoric and hydrochloric acid have a variable effect on the diarrhœa. Adrenaline and aminophylline may be unavailing in the severe bronchospasm encountered at operation. Digitalis is not helpful in cases of right-sided heart failure and may increase the diarrhœa and nausea. Orally administered diuretics and mersalyl are helpful for the control of the œdema.

Prognosis.

Carcinoid tumours grow very slowly and patients may live as long as 20 years after symptoms have developed (Mallory, 1940). With inoperable carcinoids, the immediate prognosis is not necessarily poor. Thorson (1958) has reported a series of patients who were operated upon with liver metastases, who had a survival rate of 67% after one year and 50% three years later.

A malignant carcinoid of the pancreas with unusual features and a prolonged survival has been reported (Williams, 1960).

Because of the rapid development of this man's large hepatic metastases and his cardiac lesions, it is not thought that his prognosis is good.

Conclusion.

A classical case of malignant metastasizing carcinoid is reported. The diagnosis was confirmed histologically and by the finding of increased amounts of 5 HIAA in the urine.

The response to a new drug, alpha-methyl-dopa, is reported.

Acknowledgements.

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References.

CASSIDY, M. A. (1930), "Syndrome of Flushing of the Face after Hot Drinks, Meals or Alcohol Associated with Borborygmi, Diarrhœa, Dyspnœa and Pulmonary Stenosis", *Proc. roy. Soc. Med.*, 24: 139.

ERSPAMER, V., and ASERO, B. (1952), "Identification of Enteramine, Specific Hormone of the Enterochromaffin Cell System, as 5-hydroxytryptamine", *Nature (Lond.)*, 169: 800.

JONES, I. S. M. (1957), "Malignant Argentaffinoma with Flushing but without Widespread Secondary Deposits", *Lancet*, 2: 892.

JOSEPH, M., and TAYLOR, R. (1960), "Argentaffinoma of the Lung with Carcinoid Syndrome", *Brit. med. J.*, 2: 568.

LUDWIG, G. D. (1960), "Inhibition of 5 HIAA Excretion by INH in a Patient with Malignant Carcinoid", *Clin. Research*, 8: 30.

MACDONALD, R. A. (1956), "Studies of 356 Carcinoids of the Gastro-Intestinal Tract", *Amer. J. Med.*, 21: 867.

MACDONALD, R. A., and ROBBINS, S. L. (1957), "Pathology of Heart in Carcinoid Syndrome", *Arch. Path.*, 63: 103.

MAGALINI, S. I., and STEFANINI, M. (1956), "Platelets: Relationship of Platelets to Activity of 5-Hydroxytryptamine Creatinine Sulphate", *Proc. Soc. exp. Biol. (N.Y.)*, 92: 788.

MALLORY, T. B. (1940), "Case Records of the Massachusetts General Hospital, Case 26262", *New Engl. J. Med.*, 222: 684.

MASSON, P. (1928), "Carcinoids (Argentaffine Cell Tumours) and Nerve Hyperplasia of the Appendicular Mucosa", *Amer. J. Path.*, 4: 181.

OBERNDORFER, S. (1907), *"Karzinoide Tumoren des Dunndarins"*, *Frankfurt. Z. Path.*, 1: 426.

PEART, W. S., ANDREWS, T. M., and ROBERTSON, J. I. S. (1961), "Carcinoid Syndrome: Serotonin Release Induced with Intravenous Adrenalin or Noradrenalin", *Lancet*, 1: 577.

PERNOW, B., and WALDENSTROM, J. (1957), "Determination of 5-Hydroxytryptamine, 5-Hydroxyindole Acetic Acid and Histamine in Thirty-Three Cases of Carcinoid Tumor (Argentaffinoma)", *Amer. J. Med.*, 23: 16.

RAPPORT, M. M., GREEN, A. A., and PAGE, I. H. (1948), "Partial Purification of the Vasoconstrictor in Beef Serum", *J. biol. Chem.*, 174: 735.

REID, G., and RAND, M. (1952), "Pharmacological Actions of Synthetic 5-Hydroxytryptamine (Serotonin, Thrombocytin)", *Nature (Lond.)*, 169: 801.

REINGOLD, I. M., and ESCOVITZ, W. E. (1960), "Metastatic Cutaneous Carcinoid: Report of a Case of Functioning Malignant Carcinoid", *Arch. Derm.*, 82: 971.

RESNICK, R., and GRAY, S. (1960), "Serotonin Metabolism and the Carcinoid Syndrome: A Review", *Med. Clin. N. Amer.*, 44: 1323.

ROBERTSON, J. I. S., and ANDREWS, T. M. (1961), "Free Serotonin in Human Plasma: Quantitative and Qualitative Estimation", *Lancet*, 1: 578.

SJOERDSMA, A. (1959), "Serotonin", *New Engl. J. Med.*, 261: 181, 231.

SJOERDSMA, A., OATES, J. A. ZALTZMAN, P., and UNDENFRIEND, S. (1960), "Serotonin Synthesis in Carcinoid Patients: Its Inhibition by α-methyl-dopa, with Measurement of Associated Increases in Urinary 5-Hydroxy-Tryptophan", *New Engl. J. Med.*, 263: 585.

SJOERDSMA, A., WEISSBACH, H., and UNDENFRIEND, S. (1955), "Simple Tests for the Diagnosis of Metastatic Carcinoid (Argentaffinoma)", *J. Amer. med. Ass.*, 159: 397.

SMITH, F. H., and MURPHY, R. (1960), "Carcinoid Tumours", *Med. Clin. N. Amer.*, 44: 465.

SNOW, P., LENNARD-JONES, J. E., CURZON, G., and STACEY, R. S. (1955), "Humoral Effects of Metastasising Carcinoid Tumours", *Lancet*, 2: 1004.

STEGER, C., and AVANZINI, C. (1954), *"Ricerchi istopathologiche ed istochimiche sui carcinoidi"*, *Riv. Anat. patol.*, 7: 1091.

THORSON, A. H. (1958), "Studies on Carcinoid Disease", *Acta med. scand.*, Suppl. 334, 161: 1.

THORSON, A., BIORCK, G., BJORKMAN, G., and WALDENSTROM, J. (1954), "Malignant Carcinoid of the Small Intestine with Metastases to the Liver, Valvular Disease of the Right Side of the Heart (Pulmonary Stenosis and Tricuspid Regurgitation without Septal Defects), Peripheral Vasomotor Symptoms, Bronchoconstriction and an Unusual Type of Cyanosis: A Clinical and Pathologic Syndrome", *Amer. Heart J.*, 47: 795.

WALDENSTROM, J. (1958), "Carcinoid Tumours, Clinical Aspects", Jones, F. A. (editor), "Modern Trends in Gastro-Enterology", Series II, Butterworth, London: 92.

WILLIAMS, R. (1960), "A Metastasising Carcinoid Tumour with Unusual Features", *Brit. med. J.*, 1: 28.

SOME UNUSUAL FEATURES OF POST-PARTUM HYPOPITUITARISM.

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SINCE first described in 1914 by Simmonds and clarified by Sheehan in 1937, post-partum necrosis of the anterior pituitary lobe in both its acute and chronic forms has been reported in the literature on many occasions.

After two cases of this condition had been diagnosed at the Royal Prince Alfred Hospital, further examples were sought in the hospital records. The particular features of interest revealed by this study were: (i) the delay in diagnosis both inside and outside the hospital, with subsequent morbidity and severe risk of mortality to the patient; (ii) interesting electrocardiographic patterns which occurred in three of the cases; (iii) the presence of healed pulmonary tuberculosis in every case, either as an incidental or presenting feature.

Case I.

A female, aged 45 years, presented with a classical story consistent with some residual ovarian and suprarenal function and was treated as a case of myxœdema and iron-deficiency anæmia for 10 years without effect. She was diagnosed when presenting with bilateral pulmonary infiltration, and during treatment required hysterectomy for metropathia hæmorrhagica. She developed mild diabetes insipidus and obesity after cortisone therapy.

The patient was referred to the out-patient department of the Page Chest Pavilion of the Royal Prince Alfred Hospital when, after an attack of pneumonia, she was found to have bilateral apical pulmonary infiltration and fibrosis. She had been treated with thyroid extract for myxœdema for 10 years.

She had been in hospital for three months after the birth of her last child, having to be transfused in the immediate post-partum period. She did not lactate, her axillary and pubic hair did not grow again, and soon afterwards treatment for symptoms of myxœdema was begun. However, in the subsequent 10 years she had never really regained her former health, and because of her lethargy had needed increasing assistance from her relatives to manage her domestic duties.

She had had no loss of libido and for the previous three years had had intermittent minor vaginal blood loss every four to six weeks. There was no known contact with tuberculosis and two years before, after another attack of pneumonia, during which she was unaccountably drowsy for four days, a mass-survey chest X-ray film had been reported as clear. She had apparently completely recovered from the recent pneumonia, after which another X-ray film had been taken. For some years she had had iron tablets for her anæmic appearance, but no blood count had been done until 1957, when the hæmoglobin value was 14·7 grammes per 100 ml. and the white blood cell count was within normal limits.

Examination revealed a pale, puffy-faced woman with a slightly husky voice, but without signs of obvious myxœdema. The thyroid gland was not palpable. The blood pressure was 150/90 mm. of mercury. The visual fields were normal. Scattered expiratory rhonchi were present at both lung bases. Investigations which were performed showed that the basal metabolic rate was minus 18%, in spite of her having taken 3 grains of thyroid extract per day. The urinary output of 17-ketosteroids was 2·1 mg. per 24 hours initially, with a value of only 2·6 mg. per 24 hours after 60 units of ACTH had been given intramuscularly. The absolute eosinophil level was 325 per cubic millimetre initially, falling to 170 per cubic millimetre after 60 units of ACTH had been given intravenously over six hours. (The normal depression is at least 50%.) The hæmoglobin value was 12·8 grammes per 100 ml., and the white-cell count 6200 per cubic millimetre, with 76% neutrophils, 18% lymphocytes, 5% monocytes

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and 1% eosinophils. The erythrocyte sedimentation rate was 13 mm. in one hour (the Hawksley micro method was used, by which the normal value is less than 8 mm. in one hour). The liver function tests showed a serum bilirubin level of 0·2 mg. per 100 ml., with a serum alkaline phosphatase level of 5 King-Armstrong units per 100 ml.; the Sputum and gastric aspiration specimens revealed no tubercle bacilli, either by direct smear or culture.

After the lack of response to intramuscular injections of ACTH it was decided to use the intravenous infusion technique on the grounds that it was more satisfactory, owing to the irregularity of absorption of the intra-

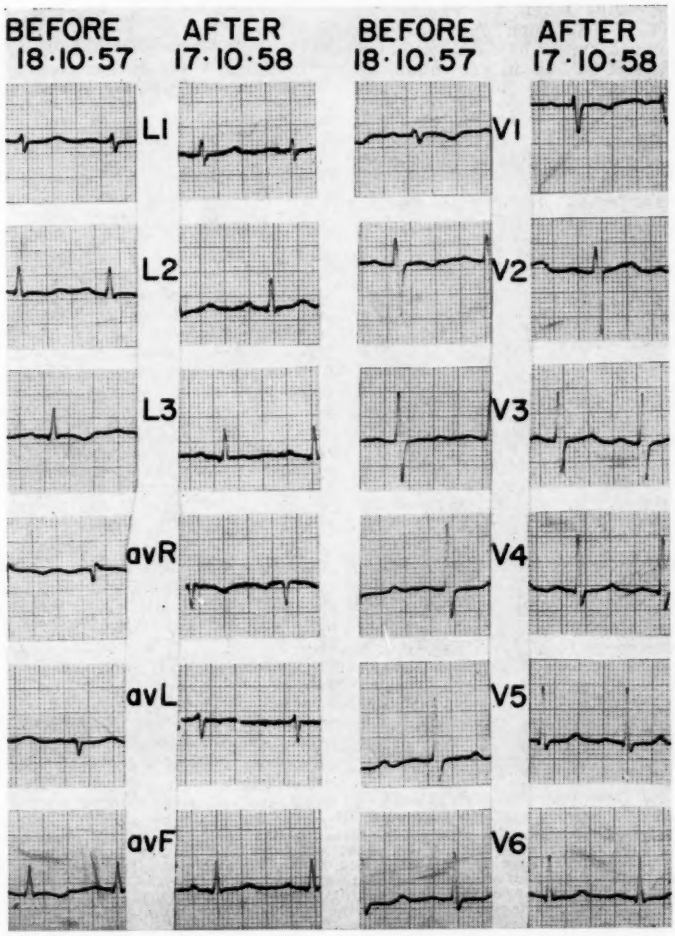

FIGURE I.

Electrocardiogram of Case I. This illustrates the complete resolution of an abnormal electrocardiogram with treatment. Before treatment (18.10.57), the voltage is within normal limits, with biphasic and inverted *T* waves present in leads II, III, *a*VF and V_1 to V_4, with normal *T* waves in the other leads. The rate is 84 per minute. After treatment (17.10.58) the tracing is normal, apart from a flattened *T* wave in lead III; the rate is 88 per minute.

thymol turbidity test gave a strongly positive result and the zinc sulphate turbidity test gave a result of 12 units (normal 2-6 units). A glucose tolerance test resulted in a flat curve, with a peak of 115 mg. per 100 ml. at one hour. Estimations for serum cholesterol and serum hydroxycorticosteroid levels were not performed, and neither was a fractional test meal or radiographic examination of the skull. An electrocardiogram (Figure I) was reported on as follows:

> The voltage is within normal limits with a rate of 84 beats per minute. Biphasic and inverted *T* waves are present in leads II, III, *a*VF, V_1 to V_4, with normal *T* waves in other leads.

muscular dose. Forty units of ACTH were given in 500 ml. of a 5% solution of glucose in distilled water over four hours. Five hours after the drip had been suspended an acute allergic reaction developed, with asthma, mental confusion, shivering and hyperpyrexia. Cortisone was given intravenously, with immediate response, the temperature of 102° F. returning to normal within four hours. As a result of this complication, the urinary 17-ketosteroid output after intravenous ACTH therapy could not be assessed.

These results appeared to indicate that the patient was suffering from Sheehan's syndrome, with the thyroid dysfunction being predominant. The following treatment was

given: ethinyl œstradiol (0·01 mg. twice daily), cortisone (12·5 mg. twice daily) and thyroid extract (1 grain three times a day). Although the dose of cortisone was such that it supplied no more than the normal physiological needs of the body, it was also considered necessary in the presence of a history of probable active tuberculosis in the previous two years, to administer isonicotinic acid hydrazide (300 mg. per day). After two months of this treatment severe vaginal bleeding began, for which total hysterectomy was required. (Dilatation and curettage two months before had revealed an atrophic endometrium, from which insufficient material for section was obtained.) The specimen showed changes consistent with cystic glandular hyperplasia with large dilated glands. The ovaries were fibrotic, with a number of germinal inclusion cysts in the cortex. Under careful cortisone cover, the patient's post-operative course was quite uneventful.

After a year of treatment the patient's condition had improved vastly, so that she could manage her home duties without assistance. However, she had gained two stone in weight and had noticed that she drank at least six pints of fluid per day, with a corresponding urinary output.

A second electrocardiogram (Figure I) showed the *T* wave changes to have almost completely resolved, flattening in Lead III being the only residuum. Serial X-ray films of the chest had shown no change.

Case II.

The patient, aged 39 years, presented with a classical post-partum story consistent with slight suprarenal function remaining. She had been treated for a recurrent macrocytic anæmia. Associated with unrecognized myxœdematous symptoms, there had been several attacks of hypothermia. Active pulmonary tuberculosis had occurred three years previously and she had more recently complained of angina pectoris.

The patient was first examined at the Royal Prince Alfred Hospital in September, 1949, when she was admitted for investigation of a morbilliform rash, for which no cause was found. Her history is a long one and is best considered in sections.

Hæmatological History.

In March, 1949, she was given a course of liver injections by her local doctor for anæmia, the details of which are unknown. On her admission to hospital later in the year a blood count revealed a hæmoglobin value of 14·4 grammes per 100 ml., with a colour index of 1·07. There was some anisocytosis and a white cell count of 10,600 per cubic millimetre, with 37% neutrophils, 42% lymphocytes, 8% monocytes and 13% eosinophils.

In 1952, when she first attended the thoracic out-patient department, the blood count was as before, with an erythrocyte sedimentation rate of 15 mm. in one hour. Later in the year macrocytosis was again noted, with a colour index of 1·14. There were no signs of subacute combined degeneration, but a histamine-fast achlorhydria was demonstrated. Numerous blood counts were performed after this, with the hæmoglobin value never falling below 11 grammes per 100 ml., the erythrocyte sedimentation rate being always between 11 and 15 mm. in one hour, and intermittent anisocytosis being present.

Thoracic History.

In 1952 the patient was referred to the thoracic out-patient department, when her son, aged 12 years, was found to have a positive Mantoux reaction. She had been

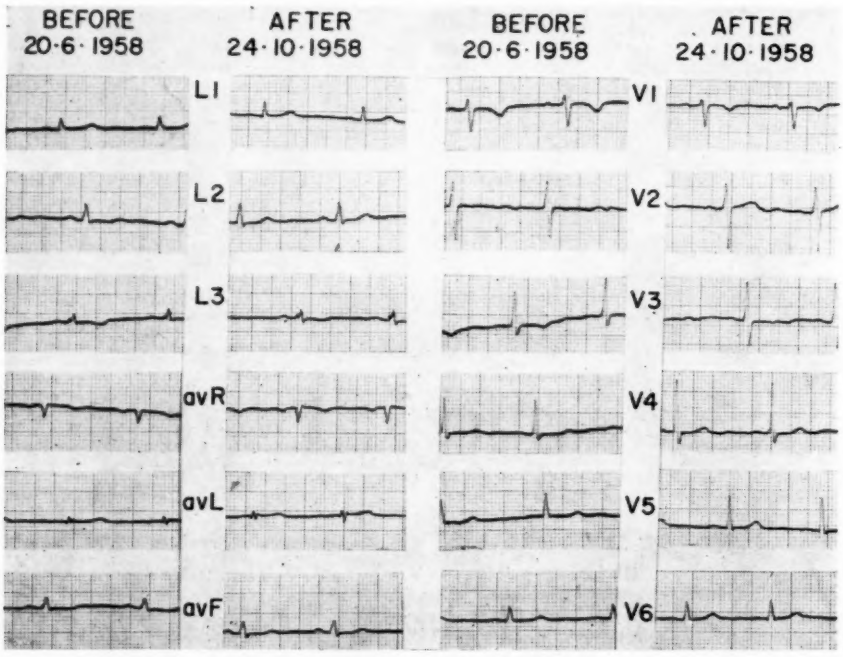

FIGURE II.

Electrocardiogram of Case II. This illustrates partial resolution of an abnormal electrocardiogram with treatment. Before treatment (20.6.58) the voltage is low, with *T* waves biphasic or inverted in leads II, III, aVF and V_1 to V_3, and normal *T* waves in the other leads. The rate is 60 per minute. After treatment (24.10.58) the *T* waves have become upright in leads II, aVF and V_2, but are still inverted in leads III and V_3. The voltage has increased slightly; the rate is 64 per minute.

nursing her tuberculous stepfather for some time. Examination of her sputum revealed no tubercle bacilli, the Mantoux reaction was positive and, although an X-ray film of her chest two years before had been clear, a right-sided apical infiltration was detected. She has been followed up ever since, never having drug therapy and with no change in the radiological picture up to the time of writing.

Cardio-Vascular History.

In March, 1958, the patient began to experience classical angina pectoris; her electrocardiogram (Figure II) showed *T* waves which were biphasic or inverted in leads II, III, *a*VF and V1 to V3, but a normal *T* wave pattern in other leads. The rate was 60 per minute, with low voltage throughout.

Endocrine History.

As part of a policy in the cardiac clinic to follow up abnormal cardiograms in young people, she was examined, and when the skin of her legs was found to be dry, the following story emerged. After the birth of her last child 17 years before she had lost enough blood to require transfusion and subsequently had had complete amenorrhœa, with no regrowth of pubic hair. In recent years she had noticed listlessness, cold intolerance and a hoarse voice, as well as dry skin and hair. In 1954, for no apparent reason, she had had an attack in which she felt very cold and then began to shiver uncontrollably in spite of many blankets. She passed into a light coma, from which she could be roused temporarily, remaining thus for four days before spontaneous recovery. In the ensuing four years she had two minor attacks of a similar nature. She was admitted to the Page Chest Pavilion of the Royal Prince Alfred Hospital in May, 1958, for investigation, with the following results. A four-day course of ACTH therapy (intramucular and intravenous) caused a significant fall in the absolute eosinophil count, with no response in the urinary 17-ketosteroid level. The sodium/potassium ratio as suggested by Stacy (1958) was not studied. The water-load test showed that after an intake of 1200 ml. of water at 8 a.m., only 60 ml. of urine were passed in the next three hours. After 100 mg. of cortisone being given orally at 5 a.m., a total of 900 ml. of urine was passed. The basal metabolic rate on two occasions was minus 24%. The serum cholesterol level was 280 mg. per 100 ml., with blood urea and liver function tests giving results within normal limits. An electroencephalogram showed slowing of basic rhythms, with 8 to 9 cycles per second alpha rhythm. Sputum examined on five occasions revealed no tubercle bacilli. The hæmoglobin value was 11·2 grammes per 100 ml., with some anisocytosis, slight central pallor and a white cell count of 8800 per cubic millimetre, of which 67% were neutrophils, 21% lymphocytes, 4% monocytes and 8% eosinophils. The erythrocyte sedimentation rate was 13 mm. per hour. The electrophoretic pattern was within normal limits.

It was thought that the results were consistent with a diagnosis of Sheehan's syndrome, with some residual activity of the suprarenals. The lack of response of the 17-ketosteroids may well have been overcome by a longer course of ACTH.

After these investigations the patient was referred to the Endocrine Clinic for the institution of drug therapy. When she attended there 10 days later she had had one of the "turns" mentioned before, but which she was able to describe in more detail owing to its recent occurrence. Two days after her discharge from hospital she had noticed a feeling of malaise with associated vomiting, occasional liquid motions and marked thirst. After several hours she had become very cold, with violent shivering and then drowsiness leading into light coma. After her spontaneous recovery she felt very tired and noticed that she passed large amounts of urine. She was placed on a regime of therapy including thyroid extract, œstrogens and cortisone, isonicotinic acid hydrazide cover not being used in her case as her tuberculosis was more remote. After three months of treatment her energy had increased and her condition had improved generally, with her angina being less marked in severity and frequency. Like the patient in Case I, she had gained weight (one stone) and had shown moderate polydipsia and polyuria (7 to 8 pints per day). The electrocardiogram (Figure II) showed that the *T* wave had become upright in leads II, *a*VF and V2, but still inverted in leads III and V3. There was slight generalized voltage increase.

As both these cases had evaded diagnosis for several years, it was decided to review the in-patient hospital records of all cases of myxœdema. In the years 1950 to 1956, three patients were found who had suffered from the syndrome, one of whom had been labelled as suffering from myxœdema of primary origin. A striking fact was that in only two of the 43 patients diagnosed as having myxœdema in this time was any note made that pituitary function had been assessed.

An analysis of the three cases is presented in sufficient detail to reveal again the same pattern of delayed diagnosis.

Case III.

A woman, aged 52 years, presented with a typical post-partum story, followed by the delayed occurrence of Sheehan's syndrome. She had had three attacks of suprarenal deficiency complicated by mental deterioration.

At the age of 24 years the patient had a severe post-partum hæmatemesis, for which her local doctor "would have liked to have given her a bucket of blood". However, she had lactated normally, and although her menses did not return for 12 months, she then retained them until the age of 30 years. At this time she developed symptoms of cold intolerance and lethargy which, eight years later, were diagnosed as being due to myxœdema. Thyroid extract therapy failed to produce any improvement, and she also developed an anæmia which was unaffected by injections of iron and liver extract.

At the age of 42 years she was admitted to another hospital for blood transfusion, but there developed a suprarenal crisis, so that the diagnosis of Sheehan's syndrome was finally made. Treatment with "Eschatin" and thyroid extract resulted in a considerable diminution in her symptoms.

At the time of this admission a right apical opacity was present in the X-ray film of the chest, which was felt to be consistent with chronic tuberculosis.

She progressed very well for several months, but then consulted another doctor who, because of the chest lesion, suspended the "Eschatin" therapy and recommended sanatorium treatment. She was unable to follow this advice for family reasons, but remained well until five years later, when she again developed symptoms of listlessness, anorexia and weight loss in spite of continued thyroid extract intake.

She tolerated these symptoms for two years, but at the age of 49 years she was admitted to the Royal Prince Alfred Hospital with a three-day history of diarrhœa, vomiting and dehydration. The diagnosis of Sheehan's syndrome was made a second time, and results of the following investigations were of particular interest. The chest X-ray film was still apparently unchanged from the one taken seven years previously, with an area of fibrosis in the right apex. An electrocardiogram (Figure III) showed low-voltage complexes at a rate of 90 per minute, and a *PR* interval of 0·26 second in all leads. The *T* wave was flattened, with a small upright *U* wave in leads II, III, *a*VF, V4 and V5. The serum potassium level at the time of this electrocardiogram was 3·8 mEq/l.

She was given 12·5 mg. of cortisone acetate twice daily with one grain of thyroid extract three times a day. This regime was to be continued. She did not return to medical supervision until 18 months later, when she was again semicomatose and gave a history of diarrhœa, drowsiness and confusion. She apparently had taken her drugs for only one month after her discharge from hospital.

On her admission to another hospital (Pascoe and McGuinness, 1959; Case D), examination of her blood revealed a serum potassium level of 3·6 mEq/l., a sodium level of 125 mEq/l. and a chloride level of 98 mEq/l. The blood glucose level was 52 mg. per 100 ml. and her Mantoux reaction was negative (1:1000). An electrocardiogram was not done.

Hormone treatment, oral salt and potassium alone were given and her condition improved, but she was discharged depressed, hallucinated and mildly confused.

An X-ray film of the chest showed bilateral hilar calcification and a right mid-zone infiltrate, the latter clearing whilst she was in hospital. An electrocardiogram was not done. She was discharged after three weeks on a regime of three grains of thyroid extract per day, and was lost to the hospital records thereafter.

When further inquiry was made to her local doctor in 1958, it was found that her condition had failed to improve, and she had developed an anæmia resistant to both iron and liver injections. She had been admitted to a suburban

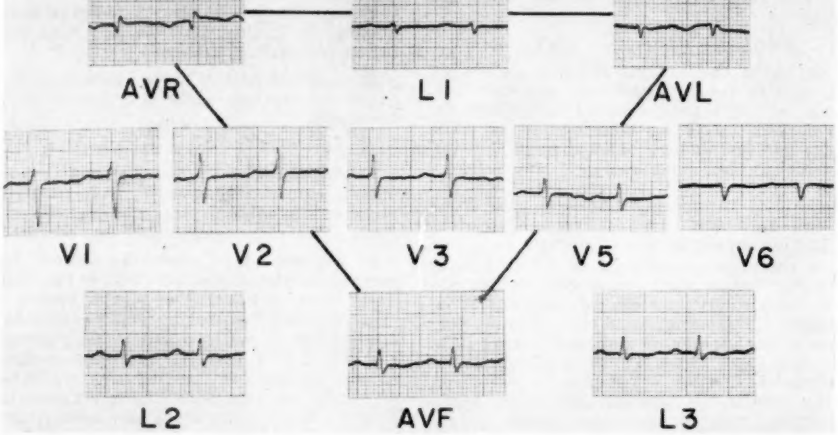

FIGURE III.

Electrocardiogram of Case III. This illustrates an electrocardiogram showing many features of hypoadrenalism and/or myxœdema. Low-voltage complexes are present throughout, with a rate of 90 per minute. The *PR* interval is 0·26 second, representing first-degree heart block. In all leads the *T* wave is flattened, with small upright *U* waves in leads II, III, *a*VF, V_4 and V_5.

This case represents the late onset of the full picture of Sheehan's syndrome with an initial predominance of the thyroid and ovarian elements. Three major attacks over the years in which suprarenal deficiency predominated caused progressive irreversible cerebral changes, probably secondary to hypoglycæmia, these making adequate treatment impossible. Unfortunately, it was not possible to repeat the Mantoux test after the patient had been on cortisone therapy for a time, but in view of the chest X-ray film, this patient almost certainly represents the phenomenon (Truelove, 1957) by which age, infection or suprarenal deficiency may depress the Mantoux reaction, this being reversed by small doses of cortisone.

Case IV.

A female, aged 49 years, with a typical story was undiagnosed for three years and had a dramatic improvement when cortisone therapy was commenced.

The patient was admitted to the Royal Prince Alfred Hospital in 1954 with a story of vomiting, diarrhœa and drowsiness for three days, associated with a severe cold. She was unable to speak English, but her friends said that "she had never liked work". Clinical findings and results of tests were thought to be consistent with severe myxœdema, but the significance of four vital clues was not recognized. These were as follows. The blood pressure was 80/60 mm. of mercury. Her temperature, although 100·6° F. on admission, never rose above 98° F. subsequently, and was between 96° F. and 97° F. most of the time. A mid-line abdominal scar was present, through which a hysterectomy had been performed in Hungary in 1947 for excessive post-partum hæmorrhage due to fibroids. The serum cholesterol level was only 170 mg. per 100 ml., this low level being a feature of the hypothyroidism of pituitary origin.

hospital for investigation, and it was there that the true nature of her illness was recognized.

She had been given prednisone (not cortisone), with the immediate loss of her troublesome leg œdema, and with a return of her energy. An electrocardiogram taken subsequently was within normal limits.

A feature of this case was the similarity of the patient's facies to those of the patient in Case I. The same puffy, almost waxy, appearance which is characteristic of this form of myxœdema was present, and this, once recognized, could easily be used for the spot diagnosis of this condition.

Case V.

A female, aged 49 years, presented with a typical story, with suprarenal function preserved as shown by her ability to survive total hysterectomy without cortisone therapy.

After the birth of her only child at the age of 26 years, the patient had had a manual removal of the placenta, associated with a severe post-partum hæmorrhage. Her menses had not returned, her pubic hair had not grown again, and she had noticed the winters to be progressively more severe. However, she had been able to manage her domestic duties without difficulty. At the age of 49 years she was admitted to King Geogre V Hospital for investigation of irregular vaginal bleeding, having been taking thyroid extract (one grain daily) and dienœstrol (0·3 mg. twice daily) for the previous six years.

She was found to have an early adenocarcinoma of the fundus uteri, for which total hysterectomy was performed. Prior to operation the blood pressure was 130/95 mm. of mercury, the basal metabolic rate was minus 35% and the urinary output of 17-ketosteroids was 8·5 mg. per 24 hours. A chest X-ray film was not taken. Although the operation was performed without cortisone cover, the immediate

post-operative period was uneventful, and after her discharge from hospital she remained well on treatment with thyroid extract alone.

Discussion.

Hæmatological Aspects.

Three of the five patients had a refractory anæmia at some stage in their histories—one of unknown nature, one macrocytic and one iron deficient. In Case II an intermittent eosinophilia was a marked feature, while the "anæmia" of Case I was probably a mirror of the patient's complexion rather than of her hæmoglobin level. In Case II there was a persistent elevation of the erythrocyte sedimentation rate in the absence of any infective cause, with the normal electrophoretic pattern, serum fibrinogen level and liver function test results not being of assistance in the elucidation of the mechanism of this.

In the reports on the anæmia of panhypopituitarism (Whitby and Britton, 1957; Daughaday *et alii*, 1948; Sheehan and Summers, 1949) no agreement has been reached as to the exact mechanism of the varying pictures which are known to be possible. All the target organs of the pituitary have been shown to affect erythropoietic function, but again the mechanism is incompletely explained. To add to the confusion, the possibility of an erythropoietic factor from the pituitary, as well as an indirect effect via an influence on the intrinsic factor of the stomach, has been postulated.

However, in the practical management of the patient, adequate doses of thyroid extract, cortisone and œstrogens result apparently in a normal blood count in the majority of cases.

Thoracic Aspects.

In four of the cases, chest X-ray films showed healed tuberculosis, and in the fifth no X-ray film was taken. In Cases I and II the period of active tuberculous infection could be definitely related to a time when the clinical features of panhypopituitarism had developed.

This association can be no coincidence, and is a reflection of the lowered resistance of these patients to all forms of external stress. It has also been found in a woman, aged 45 years, who developed symptoms of hypopituitarism at the age of 25 years, two years after deep X-ray therapy for acromegaly. At the age of 36 years she developed active pulmonary tuberculosis which responded to treatment, and when she was 45 years old a diagnosis of post-radiation hypopituitarism was finally made when she experienced cramps, diarrhœa and cold intolerance in spite of thyroid treatment.

Although the evidence of tuberculosis in all four patients of this series who underwent radiological examination of the chest suggests that active pulmonary disease should be sought in every case, experience in the use of cortisone of replacement level only in tuberculosis and Addison's disease has shown that no breakdown, even of active foci, need be expected in these patients on the institution of therapy (Sanford and Favour, 1956). However, in spite of this reassurance, it is certainly wise to follow the patient carefully with serial chest X-ray films.

There are two other associations of tuberculosis with pituitary function which are of interest.

Shuster (1957) has shown in a series of seven patients with advanced active chronic pulmonary tuberculosis, that the Addisonian features noted were due to functional insufficiency of the ACTH-producing cells alone, rather than to a primary suprarenal defect. In his cases intravenous injections of ACTH produced a normal response from the suprarenals, and at autopsy no demonstrable change was found in the pituitary.

Another possible association has been reported by Oliver (1952) in the case of a male, aged 52 years, who developed headache, vomiting and anorexia. He was thought to have tuberculous meningitis with basal adhesions and was treated accordingly. However, when given 10 units of insulin to stimulate his appetite he became comatose and died. Autopsy revealed active apical pulmonary tuberculosis (which had been missed on the plain X-ray film), combined with an isolated tuberculoma of the pituitary gland.

Cardiac Aspects.

It would be satisfying to be able to recognize a characteristic electrocardiogram for the combined myxœdema and hypoadrenalism of panhypopituitarism, but, as can be seen from Table I (Somerville *et alii*, 1951), the effects of these two conditions on the electrocardiogram overlap and there are no constant clear-cut features specific to either.

TABLE I.

Electrocardiographic Features of Hypoadrenalism and Myxœdema.

Feature.	Hypoadrenalism.	Myxœdema.
Abnormal electrocardiogram.	50% of cases.	100% of cases.
Pulse rate	Normal or rapid.	Usually slow.
PR interval ..	Increased.	Increased (sometimes up to 0·4 second).
QT interval ..	Prolonged.	Prolonged'
Voltage	Low.	Low (particularly of *P* and *T* waves).
RST segments ..	Depressed.	Depressed.
T waves	Flat or inverted in left ventricular leads particularly.	Flat or inverted in all leads.
U waves	May be prominent.	Not a feature.
Electrocardiograph response to thyroid extract.	——	Invariable within one month in the absence of concomitant coronary disease.

None of these changes is present in every case of the above two conditions, the *T* wave flattening or inversion being the most frequent in both. Although a heart rate which is not slow does not exclude a diagnosis of myxœdema, it should raise the suspicion that a more widespread disorder may be present.

The electrocardiogram of Case III showed an absence of bradycardia, combined with a *U* wave, which, while not of high amplitude, when compared with the voltage of the other complexes is quite prominent enongh to assume significance. However, this tracing is quite consistent with hypoadrenalism alone and has nothing in it which could be used as a characteristic pattern for the diagnosis of panhypopituitarism.

In Cases I and II an atypical pattern is observed which is difficult to explain. It cannot be said that the changes are consistent with myxœdema alone, because the literature is quite unanimous that the *T* wave changes of hypothyroidism are present in all leads, and although the precise cause of this is not known (Wood, 1956), this seems logical in a disease which affects all tissues of the body. One of the recent views (Lepeshkin, 1956) suggests that both altered intracellular potassium levels and the delayed exchange of metabolic waste products between the myocardium and the capillaries are the basis of this change.

How then can we explain these two electrocardiograms? In Case II the presence of angina pectoris makes it seem reasonable to suggest that these are ischæmic changes, and this is confirmed by the incomplete response to adequate hormone treatment.

In addition, it can be said that there is a coving of the *ST* segments associated with the *T* wave inversion. This is a change which is not seen in myxœdema and which suggests myocardial ischæmia rather than strain due to the sparing of V5 and V6 in both cases (Table II).

Case II resolved then to the problem of a woman, aged 39 years, with a serum cholesterol level almost within normal limits for her age group, ischæmic heart disease and Sheehan's syndrome. It seems probable that the last two are connected, but it is difficult to postulate any mechanism for it.

Case I further complicates any concept that Sheehan's syndrome may predispose to ischæmic heart disease, for in this patient the *T* wave changes are identical with those of Case II, but there was no angina, and treatment resulted in resolution of the electrocardiographic picture. The response to treatment in this patient is quite consistent with the electrocardiographic abnormality being caused by the endocrine disturbance alone.

From this discussion no definite conclusions can be drawn as to the ætiology of these changes, but the practical point remains that the cardiologist, being aware of the pattern described, may be able to suspect this condition if not actually to diagnose it.

TABLE II.

Comparison of Case I and Case II with Uncomplicated Myxœdema.

Feature.	Case I.	Case II.	Typical Myxœdema Uncomplicated by Coronary Disease.
Heart rate ..	80 per minute.	60 per minute.	Bradycardia (usually).
QRS voltage ..	Low.	Low.	Low.
ST segment ..	Cove plane in Leads II, III, *a*VF and V1 to V3.	Cove plane in Leads II, III, *a*VF and V1 to V3.	Depressed or normal.
Angina pectoris ..	Absent.	Present.	Absent.
Relief of pain with treatment.	——	Partial.	——
Response of electrocardiograph to treatment.	Yes.	No.	No.

Endocrine Aspects.

In 1937 Sheehan described 11 acute cases and one chronic case of post-partum necrosis of the anterior pituitary and resolved the confusion that Simmonds had created in 1914 by stressing the cachexia of his patient. Since this time it has gradually become customary to refer to this post-partum variety of hypopituitarism as Sheehan's syndrome, and there have been many articles describing cases, particularly those with coma (Caughey, 1954; Sheehan, 1955; Pascoe and McGuinness, 1959). However, it is hoped that the presentation of this series will again bring it to mind, for, as we have seen, the correct diagnosis of these patients may fall to the general practitioner (as in the case of a patient with anæmia or myxœdema), the chest specialist (in the case of tuberculosis, acute or chronic), the psychiatrist (when the patient exhibits anxiety, depression or mental deterioration) or the resident medical officer (in the case of a patient in coma), to mention some of the possibilities.

These patients are particularly prone to become comatose, this being the mode of presentation in Case III. There are several possible mechanisms involved (Caughey and Garrod, 1954), best summarized as follow. Suprarenal mechanisms include: (i) Addisonian crisis; (ii) hypoglycæmia; (iii) lack of response to stress—for example, drugs, anæsthesia, operations and infections; (iv) water intoxication. Disordered functions of the higher centres, that is, the hypothalamus, thalamus or mid-brain, include myxœdema coma, hyperthermia, hypothermia, hypersomnia and cerebral anoxia of vasovagal origin.

The origin of the last group of conditions is, of course, only tentative, but the five conditions mentioned under disordered function of higher centres certainly occur in hypopituitarism and, except in the case of myxœdema coma, cannot be accounted for by direct hormone influence, but rather by an indirect effect on the higher centres. However, we should not expect to find these patients always semi-comatose because, as in Case II, they may appear quite normal superficially. Again, the fact that only one of the pituitary end organs is mainly affected (as in Case V) should not throw doubt on the diagnosis. Pituitary dysfunction has many possible combinations, and it is the duty of the clinician to gain a complete assessment of the patient, using not only the tests available, but also the clinical response to treatment. The patient who is predominantly and obviously myxœdematous provides an easy diagnosis and has only to be asked when her last period occurred. However, as these cases are often not affected in an obvious fashion, it is important to use in every patient what must be regarded as the most sensitive objective index of myxœdema—the texture of the skin, particularly of the legs.

It is certain that there must be many cases of mild myxœdema (pituitary or otherwise) remaining undiagnosed in any population. It is a well-known fact that even marked myxœdema may be overlooked, and so these early cases represent a definite challenge which can be overcome only by including a precise assessment of the skin texture in the routine examination of every patient, thus avoiding missing what in retrospect is often an obvious diagnosis.

It may be expected that the incidence of this syndrome will gradually decrease with the improved management of obstetrical emergencies, but at least for the next 10 years the alert diagnostician should always bear it in mind in order to save these patients many years of misery.

Summary.

Five cases of Sheehan's syndrome are reported, two of these patients being well known to the writer, the remaining three being obtained from a retrospective survey of the records of the Royal Prince Alfred Hospital and then followed up as far as possible.

An electrocardiographic pattern which may be suggestive of the disease is reported.

The common association with tuberculosis is noted, as are other modes of presentation.

The delayed diagnosis of this condition is emphasized, the solution to this being the suspicion of it in every case of myxœdema, particularly in patients under the age of 45 years.

Acknowledgements.

Grateful acknowledgement is made to Dr. K. Harrison and Dr. H. Fleming for their assistance and encouragement in the preparation of this paper. The general superintendent and honorary medical officers of the Royal Prince Alfred Hospital, Camperdown, Sydney, are thanked for permission to publish details of the cases, as is the medical superintendent of Sydney Hospital for later details of Case III.

References.

CAUGHEY, J. E. (1954), "Hypopituitarism and Some Disturbances of Consciousness Associated with it", *Aust. Ann. Med.*, 3: 26.

CAUGHEY, J. E., and GARROD, O. (1954), "Coma and Allied Disturbances of Consciousness in Hypopituitarism", *Brit. med. J.*, 2: 554.

DAUGHADAY, W. H., WILLIAMS, R. H., and DALAND, G. A. (1948), "The Effect of Endocrinopathies on the Blood", *Blood*, 3: 1342.

LEPESHKIN, E. (1951), "Modern Electrocardiography", Williams and Wilkins, Baltimore, 1.

OLIVER, L. C. (1952), "Pituitary Tuberculoma", *Lancet*, 1: 698.

PASCOE, B. J., and MCGUINNESS, A. E. (1959), "Post Partum Panhypopituitarism", MED. J. AUST., 2: 635.

SANFORD, J. P., and FAVOUR, C. B. (1956), "The Interrelationships between Addison's Disease and Active Tuberculosis", *Ann. intern. Med.*, 45: 56.

SHEEHAN, H. L. (1937), "Post-Partum Necrosis of the Anterior Pituitary", *J. Path. Bact.*, 45: 189.

SHEEHAN, H. L., and SUMMERS, V. K. (1949), "The Syndrome of Hypopituitarism", *Quart. J. Med.*, 18: 319.

SHEEHAN, H. L., and SUMMERS, V. K. (1952), "Treatment of Hypopituitary Coma", *Brit. med. J.*, 1: 1214.

SHEEHAN, H. L. (1955), "Coma in Hypopituitarism", *Brit. med. J.*, 2: 1022.

SHUSTER, S. (1957), "The Functional Hypopituitarism of Advanced Chronic Pulmonary Tuberculosis", *Brit. J. Tuberc.*, 51: 279.

SOMERVILLE, W., LEVINE, H. D., and THORN, G. W. (1951), "The Electrocardiogram in Addison's Disease", *Medicine (Baltimore)*, 30: 43.

STACY, B. D. (1958), "The Use of ACTH in the Diagnosis of Addison's Disease", MED. J. AUST., 2: 482.

TRUELOVE, L. H. (1957), "Enhancement of Mantoux Reaction Coincident with Treatment with Cortisone and Prednisolone", *Brit. med. J.*, 2: 1135.

WHITBY, L. E. H., and BRITTON, C. J. C. (1957), "Disorders of the Blood", Eighth Edition, Churchill, London: 298.

WOOD, P. (1956), "Diseases of the Heart and Circulation", Second Edition, Eyre and Spottiswoode, London: 891.

CHRONIC DIARRHŒA DUE TO STRONGYLOIDES STERCORALIS.

By G. SIBTHORPE, M.B., B.S., T.D.D. (Cardiff), *Rabaul.*

Clinical Record.

THE patient, an ex-serviceman aged 54 years, was found to have amœbic dysentery in 1945. This was treated for four months and apparently cleared, although the patient states that his bowel actions never returned to normal, but remained loose, and that he had frequent mild attacks of diarrhœa.

On demobilization he was found to have an ulcer in the sigmoid colon. Extensive investigations failed to reveal any *Entamœba histolytica*. The ulcer was excised after 10 months' conservative treatment, and the pathological examination revealed chronic inflammation only. Subsequently the patient continued to have attacks of diarrhœa. Owing to his occupation (he was a ship's officer) he was treated by various doctors in various parts of the world, generally with sulpha drugs or standard treatment for amœbic dysentery.

He reported to the Repatriation Department on several occasions, where repeated examinations for *E. histolytica* were performed; sigmoidoscopy and a barium-enema X-ray examination also were done several times. All these examinations failed to reveal anything abnormal. Diagnoses varied from chronic amœbic dysentery to anxiety state and achlorhydria. The patient became resigned to accepting chronic diarrhœa as a part of his normal existence.

In May, 1959, after a particularly severe attack of diarrhœa, he was persuaded to send a specimen of fæces to the Public Health Department laboratory at Rabaul. This specimen showed the presence of *Strongyloides stercoralis*.

A supply of dithiazanine iodide ("Telmid") was obtained and 600 mg. was given daily for two weeks. The response was rapid. For the first time since before the war the patient had normal, formed stools, and as yet there has been no recurrence of diarrhœa.

Discussion.

Strongyloides is reported to have a world-wide distribution. This man had long periods of war service in various parts of Papua and New Guinea, where he most certainly contracted the infection. The incidence is generally reported as low in the Pacific, but it does occur. In 1944 16 cases were reported in Australian service personnel in an army hospital in New Guinea, and Dr. A. V. G. Price, of the pathology department at Port Moresby, in a personal communication, said that while he had been looking after a laboratory in the army *Strongyloides* had been commonly found in troops serving in all parts of the Territory.

It was thought worth reporting this case as *S. stercoralis* is apparently worthy of consideration as a cause of chronic diarrhœa in ex-servicemen.

Acknowledgement.

I wish to thank the Deputy Commissioner, Repatriation Department, Brisbane, for supplying clinical notes; Dr. A. V. G. Price of Port Moresby and Dr. T. C. Backhouse of the School of Tropical Medicine, Sydney, for information; and Eli Lilly Pty. Ltd. for supplying the "Telmid".

Reviews.

How to Relax and Have Your Baby: Scientific Relaxation in Childbirth. By Edmund Jacobsen, M.D.; 1959. New York, Toronto, London: McGraw-Hill Book Company Inc. 8" × 5¼", pp. 210, with illustrations. Price: $3.95.

FROM the accomplished pen of this most prolific writer on scientific relaxation comes a book directed, not only at the mother-to-be, but at all married women, giving instructions on how to overcome the tensions which are their inevitable lot. It is perhaps a little lengthy and laboured, as is the wont of these works, since they are designed to replace the patient and painstaking instructor's verbal lessons.

Maxine is the heroine, and her true story is traced from the conception of her baby to its delivery and after. We are present at her lessons and follow her in photographs as she learns her skill.

Jacobsen maintains that it is not necessary to cultivate enthusiasm or faith in the patient, as these involve the emotions, and an emotional state is the opposite of relaxation. He believes the responsibility of accepting or refusing anæsthetic at delivery should be taken from the mother, since decision requires effort and effort is, again, the opposite of relaxation. He objects to the term "relaxation exercises", pointing out that the two words cancel each other out.

The message of the book is that a skill must be mastered—much as one would master the skills of cycling or piano-playing—and a great deal of practice must be done. At first, as each muscle group is trained to relax, residual tensions are detected in the author's surgery by the electromyograph, and the subject learns to recognize the sensation of tension and "go negative" in that part.

The author claims great success for his method, giving several case histories to support his claim, and in fact becomes quite emotional himself in describing the joys of motherhood which his method makes possible.

Tumors of the Female Sex Organs, Part III: Tumors of the Ovary and Fallopian Tube. By Dr. A. T. Hertig, M.D., and H. Gore, M.B., B.S.; 1961. Washington, D.C.: Armed Forces Institute of Pathology. 10¼" × 8", pp. 176, with many illustrations. Price: $1.40.

FASCICLE 33 of Section IX of this "Atlas of Tumor Pathology" is a uniform volume with the other monographs and is of a similar degree of excellence. A minimum of explanatory text precedes the beautifully presented photomicrographs, each with its own legend. Some macroscopic studies are given and several case histories; but the emphasis naturally is on pathogenesis and microscopic features rather than on clinical details.

At the outset the authors acknowledge the confusion existing with regard to the classification of tumours of the ovary and Fallopian tubes; they even state that their own original classification, adopted in 1955, when the fascicle was first submitted for publication, contained some inconsistencies, and suggest a "more logical" one. However, the pathologist will find his way about very well.

Clinical Obstetrics and Gynecology, Volume 4, Number 1: Obstetric Anesthesia and Analgesia. Edited by R. A. Hingson, M.D., **Vaginal Surgery.** Edited by A. F. Lash, M.D., Ph.D.; 1961. New York: Paul B. Hoeber, Inc. 9¼" × 6", pp. 304 with illustrations. Price: $18.00 per year by subscription.

MOST of the contributors to the symposium on "Obstetric Anesthesia and Analgesia", edited by Robert A. Hingson, belong to the Departments of Anesthesia or of Obstetrics and Gynecology in the Western Reserve University, Cleveland, Ohio. Professor Hingson introduces the subject with a short historical survey and summary of the extensive research in progress there.

The effects of oxytocin on the pregnant and parturient uterus, and the effects of inhalation and conduction anæsthesia in labour, are discussed by Vasicka and Kretchmer in a paper on uterine dynamics. These authors also contribute the chapter on inhalation anæsthetics. Quilligan writes on the effects of maternal anæsthesia on fœtal oxygen, and shows the value of oxygen administration during delivery. Drugs producing analgesia, sedation and amnesia, and their respective effects on mother and fœtus, are discussed by Professor Hingson, and Cull contributes an excellent chapter on conduction anæsthesia. Every aspect from psychology to complications is covered. The safety

of spinal anæsthesia is demonstrated by the record of only three maternal deaths related to the anæsthetic in 150,000 cases.

There is a chapter on management of psychorelaxation, and a pædiatrician writes on resuscitation of the new-born. Special anæsthetic problems arising in relation to the unmarried mother and the grand multipara and in cases of multiple pregnancy are also considered.

After a foreword by guest editor Abraham Lash, of Chicago, the symposium on "Vaginal Surgery" is opened with a chapter on the vaginal diagnostic procedures of colpocentesis, colpotomy, culdoscopy and colposcopy. Wolff writes on the cervix. In describing techniques of cervical biopsy and conization, he emphasizes the complications common after these minor procedures. He recommends that cervical polyps should be removed by conization, and holds that the practice of twisting off a polyp (which, with adequate follow-up, is usually accepted as satisfactory) is "of little value". William Mengert describes the Noble-Mengert rectal wall advancement operation in cases of old complete perineal tears resulting in cloaca formation.

It is refreshing to find an American advocate of the Fothergill operation. Robert E. Gordon describes the technique, and goes so far as to state that it is the operation of choice for complete procidentia. Patients are kept in hospital seven or eight days after operation.

Walters describes the ætiology and operative treatment of upper posterior vaginal herniation (enterocele).

For the third time in this series, the technique of vaginal hysterectomy as performed at the Mayo Clinic (where more vaginal than abdominal hysterectomies are done) is described here by Welch and Randall. Indications are listed, and in recent years carcinoma-in-situ runs in second place to prolapse, with hæmorrhage third. Lash describes a modification of vaginal hysterectomy to allow the removal of abnormally large uteri, in which the endometrium and a layer of subjacent myometrium are shelled out from within the main bulk, which (after division of the adnexa) is then removed.

Porges, in a description of the Schauta operation, suggests the likelihood of its increasing popularity in cases of carcinoma-in-situ, and in microinvasive Stage I cases.

Several methods of management of vaginal fistulæ are described by Falk.

There is a chapter on operations for double uterus and endometrial atresia, and Stanley Way describes his operation of radical vulvectomy.

This number ends with an interesting special article on the medico-legal aspects of psychogenic abortion, written by an obstetrician and a lawyer.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Australia in the War of 1939-1945. Series 5 (Medical): Medical Services of the R.A.N. and R.A.A.F., with a Section on Women in the Army Medical Services", by Allan S. Walker, M.D., Ch.M., F.R.A.C.P., and others; 1961. Canberra: Australian War Memorial; Sydney: Angus & Robertson Ltd. 9¼" × 6", pp. 574, with illustrations. Price: 35s.

"Management of Medical Emergencies", edited by John C. Sharpe, M.D.; New York, Toronto, London: The Blakiston Division, McGraw-Hill Book Company, Inc. 8" × 5¼", pp. 354. Price: $9.75.

"The Human Adrenal Gland", by Louis J. Soffer, M.D., F.A.C.P., Ralph I. Dorfman, Ph.D., and J. Lester Gabrilove, M.D., F.A.C.P.; 1961. Philadelphia: Lea & Febiger, Sydney: Angus & Robertson Ltd. 9¼" × 6", pp. 592, with illustrations. Price: £10 3s. 6d.

"Resuscitation of the Unconscious Victim: A Manual for Rescue Breathing", by Peter Safar, M.D., and M. C. McMahon; second edition, 1961. Sprngfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 7¾" × 4½", pp. 86, with illustrations. Price: 16s.

"Pathology of the Nervous System: A Student's Introduction", by J. H. Biggart, C.B.E., M.D., D.Sc., F.R.C.P., foreword by Professor A. Murray Drennan, M.D., F.R.C.P.E., F.R.S.E.; Third Edition, 1961. Edinburgh, London: E. & S. Livingstone. 8½" × 5½", pp. 368, with 261 illustrations. Price: 40s. net.

"Samson Wright's Applied Physiology", revised by C. A. Keele and Eric Neil, with the collaboration of John B. Jepson; Tenth Edition, 1961. London, New York, Toronto: Oxford University Press. 11" × 8½", pp. 556 with illustrations. Price: 86s. 3d.

"Myasthenia Gravis: The Second International Symposium Proceedings", edited by Henry R. Viets, M.D.; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9" × 6", pp. 708, with illustrations. Price: £11 12s.

"Hypnosis in Obstetrics: Obstetric Hypnoanesthesia", by Ralph V. August, B.S., M.D., F.A.C.O.G., F.I.C.S.; 1961. New York, Toronto, London: The Blakiston Division, McGraw-Hill Book Company, Inc. 9¾" × 7¼", pp 160. Price: $10.00.

"Functions of the Blood", edited by R. G. Macfarlane, M.A., M.D., M.R.C.S., F.R.S., and A. H. T. Robb-Smith, M.A., M.D., F.R.C.P.: 1961. Oxford: Blackwell Scientific Publications Ltd. 9" × 6", pp. 636, with illustrations. Price: £6 (English).

"Anesthesia and the Law", by C. E. Wasmuth, M.D., LL.B.; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9" × 6", pp. 106. Price: 40s.

"Clinical Obstetrics and Gynecology", Volume 4 Number 2: "Perinatal Mortality", edited by Robert E. L. Nesbitt, Jun., M.D.; "Radiation Therapy", edited by A. N. Arneson, M.D., and James F. Nolan, M.D.; 1961. New York: Paul B. Hoeber, Inc. 9½" × 6¼", pp. 287, with illustrations. Price: $18.00 for four consecutive issues, by subscription only.

"Preparation for Medical Education: A Restudy; The Report of the Committee on the Resurvey of Preprofessional Education in the Liberal Arts College, Association of American Medical Colleges", by A. E. Severinghaus, Ph.D., H. J. Carman, Ph.D., and W. E. Cadbury, Jun., Ph.D.; 1961. New York, Toronto, London: The Blakiston Division, McGraw-Hill Book Company, Inc. 8½" × 5¾", pp. 404. Price: not stated.

"The Physician in Industry", by W. P. Shepard, M.D., M.A.; 1961. New York, Toronto, London: The Blakiston Division McGraw-Hill Book Company, Inc. 8½" × 5¾", pp. 290. Price: $9.50.

"Asylum to Community: The Development of The Mental Hygiene Service in Victoria, Australia", by E. Cunningham Dax; 1961. Melbourne, Canberra, Sydney: F. W. Cheshire. 8½" × 5½", pp. 230, with illustrations. Price: 30s.

"Cross-Cultural Studies in Mental Health: 1. Identity. 2. Mental Health and Value Systems", edited by Kenneth Soddy; 1961. London: Tavistock Publications. 8½" × 5½", pp. 271. Price: 25s.

"The Serology of Conglutination and its Relation to Disease", by R. R. A. Coombs, M.R.C.V.S., B.Sc., Ph.D., A. M. Coombs, B.A., Ph.D., and D. G. Ingram, D.V.M., M.V.S.C., Ph.D.; 1961. Oxford: Blackwell Scientific Publications. 8½" × 5¾", pp. 210, with illustrations. Price: 40s. (English).

World Health Organization Technical Report Series No. 220, "Evaluation of the Carcinogenic Hazards of Food Additives; Fifth Report of the Joint F.A.O./W.H.O. Expert Committee on Food Additives"; 1961. Geneva: World Health Organization. 9½" × 6¼", pp. 36. Price: 3s. 6d.

World Health Organization Technical Report Series No. 221, "Scientific Meeting on Rehabiltation in Leprosy, Vellore, Madras State, India, 21-29 November 1960, Report"; 1961. Geneva: World Health Organization. 9½" × 6¼", pp. 37. Price: 3s. 6d.

"Miscellaneous Notes", by F. Parkes Weber, M.D., F.R.C.P., F.S.A.; twelfth series, 1961. London: H. K. Lewis & Co. Ltd. 7¼" × 5¾", pp. 8. Price: 2s. 6d.

"The Scientific Basis of Medicine: Annual Reviews 1961", sponsored by British Postgraduate Medical Federation; 1961. 8½" × 5½", pp. 342, with illustrations. Price: 40s.

"Bone: An Introduction to the Physiology of Skeletal Tissue", by F. C. McLean, Ph.D., M.D., and M. R. Urist, M.D.; second edition; 1961. Chicago: The University of Chicago Press. 8½" × 5½", pp. 262, with illustrations. Price: $6.00.

"The Facts of Mental Health and Illness", by K. R. Stallworthy, M.B., Ch.B.; third edition; 1961. Christchurch: N. M. Peryer Limited. 8½" × 5½", pp. 227. Price: 24s. (New Zealand).

"Freud and the Post-Freudians", by J. A. C. Brown; 1961. Middlesex, Baltimore, Victoria: Penguin Books Ltd. 7¼" × 4½", pp. 226. Price: 5s. 6d.

"Psychiatry: Volume 1: Principles". Part I: Personology. Part 2: General Psychiatry, by E. Eduardo Krapf, M.D.; 1961. 8½" × 5½", pp. 244 with illustrations. Price: $6.50.

"Hypertension", A Mount Sinai Hospital Monograph, edited by Milton Mendlowitz, M.D.; 1961. New York, London: Grune & Stratton. 10" × 6¾", pp. 156, with illustrations. Price: $6.50.

The Medical Journal of Australia

SATURDAY, OCTOBER 7, 1961.

FRIDTJOF NANSEN.

On October 10 we are asked to remember the centenary of the birth of a very great man. Few men have ever exemplified as clearly as did Fridtjof Nansen that really outstanding ability is not restricted to any one field. True genius illuminates any sphere of activity in which it is brought to bear. Nansen is most widely remembered today for his services to humanity as the champion of the homeless, the hungry and the oppressed during the bitter years which followed the end of World War I; and in a world in which refugee problems have taken on a perennial air, it is particularly appropriate that we should pause to remember the man who was one of the first to tackle this problem in its modern guise. In his country he is remembered as a great national hero who played an important rôle in launching his country as an independent nation, when Norway was peacefully separated from Sweden in 1905, and who brought honour to his country by his achievements in many spheres. And all over the world are scattered individuals deeply interested in Arctic and Antarctic matters who know Nansen as the great pioneer of polar exploration. In all these spheres he showed the qualities of courage, integrity and simplicity of purpose which combined to make him a pillar of strength in any adversity. To these qualities he added a clarity and depth of vision which enabled him to see at once the necessity of the moment in all its implications.

As a young man he was an athlete of considerable talent, and he excelled in skiing and skating, the sports particularly appropriate to his native land. He was early attracted to the problems of polar exploration, then in its infancy, and is remembered for two remarkable expeditions. One was the first crossing of the Greenland ice-cap, which he accomplished with five companions in 1888, and which is the subject of a fascinating account by himself. The other was his attempt to reach the North Pole by sailing his ship, the *Fram*, into the Arctic pack-ice as far as possible at a selected point, then deliberately allowing it to get frozen in, in the expectation that the drift of the ice would carry it sufficiently close to the Pole to make access across the sea ice possible. The boldness of conception of this plan was matched by the meticulous care with which it was launched and the daring spirit in which it was carried through. Nansen did not reach the North Pole, but the story of the voyage of the *Fram*, and Nansen's subsequent trek, with one companion, across the polar pack-ice is a saga which alone would make his name immortal as long as people are interested in the deeds of brave men. On his return from his polar adventures he went on with his scientific studies, a sphere in which, had circumstances been less demanding, he would undoubtedly have achieved a distinguished career. However, as already noted, he soon became involved in Norway's move for independence, and from 1905 to 1908 he was the first Norwegian Minister to London. In 1908 he became the first holder of the chair of oceanography at Oslo University, but the outbreak of war six years later once again diverted him from the academic life in which he might so easily have found personal contentment. In 1917 and 1918 he led a diplomatic mission to the United States, and from 1920 to the time of his death, on May 13, 1930, he was his country's representative in the Assembly of the League of Nations.

This decade was the period of Nansen's greatest achievement, for though he was only the representative of a small nation (this was in some ways an asset), his figure dominates the story of the work that went on in bringing relief to the millions who were homeless and destitute as a result of the upheavals of the preceding years. In 1920 he was given the task of arranging the repatriation of nearly half a million prisoners of war who had been left stranded in Siberia and other parts of Russia. In 1921 he was appointed first League of Nations Commissioner for Refugees. In this capacity he appealed in vain for an international loan to relieve the appalling famine which at that time was taking such a toll of the Russian people. This was one of his rebuffs, but before his personality and reputation all doors were open, and in other directions he was able to achieve much. In 1922 he was awarded the Nobel Peace Prize in recognition of his efforts, but for eight more years, up to the time of his death, he continued to toil in the cause of the homeless and destitute. During this time he was concerned with a succession of refugee situations, and dealt with each in the same spirit as had animated his scientific explorations. Difficulties were there to be surmounted. Nansen never hesitated to take a decision or to back a cause, no matter how unpopular. Except for his fight to find a national home for the thousands of Armenian refugees, his efforts were nearly always crowned with success. The Nansen Certificate, which was accepted as a passport by more than 50 governments, brought a ray of hope to many thousands of stateless persons who, without papers, could not obtain official recognition even of their existence. Nansen may be said to have established the precedent which was later followed, in a more formal capacity, by other Scandinavians who have also given distinguished and dedicated service, and in some cases their lives, in the cause of international peace.

Fridtjof Nansen was a great man in the sense that Vincent de Paul, Louis Pasteur, and Mahatma Gandhi were great. Each gave, drawing freely on his great talents, unstinted and selfless service in the cause of his fellow men. Nansen's services to his own country and to

humanity at large were of such a quality that they stand as a beacon to guide the generations to come in times of doubt.

THE POSSIBILITY OF HOST DEFENCES AGAINST CANCER.

ARE there host defences against cancer? This rhetorical question is the title of an article by C. M. Southam[1] which forms part of a symposium on "The Medical Aspects of Cancer" dedicated to the memory of Dr. Cornelius P. Rhoads, Director of the Sloan-Kettering Institute. The problem is considered under three headings: first, clinical observations; second, laboratory and clinical experiments; and third, the mechanisms of host defence. Southam points out that the tremendous variation in the natural history of cancer of a single histological type among different individuals is well known to experienced physicians. These variations may reflect intrinsic differences in the growth potential of cancer cells, but it is also possible that they indicate differences in the resistance of individual hosts. There are instances of the existence of cancer in apparent quiescence long before the onset of overt disease. The activity of latent metastases of long standing may be a similar phenomenon. Not only does cancer show variable aggressiveness and quiescence, but true regression may occur. Complete and permanent regressions, though rare, have been documented for many types of cancer. Several mechanisms have been invoked to explain the variability of the behaviour of cancer, without having to invoke host defence mechanisms; but Southam asserts that they have no greater factual support and are not intrinsically more plausible than the hypothesis of resistance due to host mechanisms. In the absence of proof of cancer cell autonomy, the less fatalistic hypothesis of a variable host resistance deserves equal consideration. Recent research has shown the great frequency with which cancer cells are disseminated throughout the body, and it seems clear that not every disseminated cancer cell finds a completely passive niche in which to grow. What local tissue factors are concerned? Finally, in considering clinical considerations, there is the question "Why don't we all get cancer?". In general the possibility of exposure to carcinogens is extremely variable, but even in a population undergoing apparently equal exposure to a known risk—such as sunlight, atomic bomb irradiation, radium or "Thorotrast" poisoning, aniline dyes or heavy smoking—the incidence of cancer is not uniform.

Coming to Southam's second heading, namely, experimental studies on resistance to cancer, it must be admitted that these fall far short of proving an active host defence against autochthonous cancer, but they do at least cast grave doubts on the contrary assumption that cancer is completely aloof from host controls. The trouble with experimental studies is that the material available is limited and it is difficult to establish adequate controls. The only cancer of interest to the clinician is autochthonous cancer—cancer which arises apparently spontaneously in the individual under consideration. Most experimental work has been performed on transplanted tumours in small animals and on a few human volunteers; for instance, patients with advanced neoplasms. However, for what they are worth, several experiments suggest that tumour growth can be influenced by certain treatments which have no direct effect on the tumour but have an influence on non-specific host defence mechanisms. Southam instances the work of W. T. Bradner *et alii*[2], who, working with sarcoma 180 of mice, observed that small doses of zymosan (a crude polysaccharide preparation from yeast) caused an increased rate of tumour rejection and prolonged survival of mice as compared with the untreated controls. He also discusses the extensive studies of L. Pillemer[3] and many others on properdin and other work on the possibility of host resistance to cancer cells.

Lastly, Southam turns to the broad field of basic immunology which, he believes, supplies abundant mechanisms that might participate in host defences against cancer. At present, one can only proceed on a method of trial and error. Any factor operative in host defence is of potential interest until found not to participate in the defence against cancer. What is needed is basic research into cell mechanisms that may affect cell growth and cell relationships. The mere existence of cancer cells does not explain their virulence; it is their behaviour that matters. A relevant instance is the variable behaviour of chorionic cancer. Altogether this is a most stimulating article and it is no derogation to say that its interest depends on hypotheses rather than facts. As Southam writes:

> It keeps open the only possibility for major progress in cancer prevention. . . . The theory of cancer autonomy is a Lorelei which has the alure of beautiful simplicity while the hypothesis of host defences against cancer invokes complex and nebulous concepts. But unless and until this possibility is finally disproved it should not be ignored, for that which is autonomous is irresistible but that which is in any way vulnerable can be attacked regardless of how unequal the aggressive and defensive forces may seem.

[1] *Med. Clin. N. Amer.*, 1961, 45: 733 (number 3).

[2] *Proc. Amer. Ass. Cancer Res.*, 1958, 2: 282.

[3] *Science*, 1954, 120: 270.

Comments and Abstracts.

TOWARD THE CONQUEST OF BERIBERI.

THE discovery of the cause of a disease is only one step in its eradication—although it could be an important step. That beriberi is a nutrient deficiency disease, and the broad facts concerning the distribution in foods of the substance concerned, have been fairly widely known since about the year 1910. The chemical composition of this substance, vitamin B_1 or thiamine, was finally elucidated in 1935, and by 1939 large-scale synthesis of thiamine at reasonable cost was in operation. Yet beriberi still exists in some countries today on a scale that is not inconsequential.

An American scientist, Dr. R. R. Williams, has been intimately concerned over the past 50 years with the gradual stripping of the veil obscuring the detailed character of this disease, and since World War II with attempts to find ways to eliminate it from the world. Probably no one is better qualified by such close participation in this work to write a book that can make readily available a view in perspective of the events which have revealed the cause, the cure, and the means of prevention of beriberi. In 1938 he published, with T. Spies, a book

entitled "Vitamin B_1 and Its Uses in Medicine", which still remains an indispensible source of reference to the literature about thiamine and its actions. In his latest book[1] Williams is concerned primarily with the historical facts surrounding the disease.

There are two aspects of the recent history of thiamine and beriberi that Williams has highlighted because of his close association with them. Both emphasize the fact that scientific discovery and enterprise can never be segregated from politics and law, however much one would wish that this could be so. After discoveries had been made concerning the structure and synthesis of thiamine, Williams filed patents and assigned the rights to the Research Corporation. Most of the royalties have for many years been donated to the Williams-Waterman Research Fund for the Combat of Dietary Diseases. This Fund has sustained a great deal of nutritional research in the U.S.A. and elsewhere. Scientists interested in laws concerning patents and the relation of research workers to them would find something of general interest in the section of the book dealing with this aspect of the history of thiamine.

Another subject that Williams is in a unique position to discuss arises from the sponsoring by the Williams-Waterman Fund of a plan to eliminate beriberi from the province of Bataan in the Philippines. The plan was put into operation shortly after the end of World War II, and was based on mixing with white rice a special "pre-mix" consisting of rice grains coated with a relatively high concentration of synthetic thiamine. Despite the theoretical simplicity of the plan, formidable difficulties were encountered—mostly resulting from socio-political factors. The story emphasizes the difficulties that public-health administrators may meet when they attempt to introduce changes into an established social system. Williams's book serves a useful purpose as a record of some aspects of the past history of beriberi, and undoubtedly it will be of assistance to those who will follow him, and whose turn it will be to take up arms for the conquest of this disease.

THE ORIGIN OF SYPHILIS.

THAT venereal syphilis burst upon mediæval Europe with all the virulence of a new disease in a completely unprotected population is widely accepted as an established fact, though E. H. Hudson[2] has seriously challenged this interpretation of history. It was for long popularly accepted that it was an importation brought by Columbus's sailors from central America. Then Hans Zinsser, in his entertaining book of epidemiological essays, "Rats, Lice and History", presented a plausible case for the reverse proposition—that the sixteenth century sailors brought syphilis, recently introduced to Europe from the Near East, to central America. Whatever the facts about this particular episode, both theories are incomplete, and it is possible that both are wide of the mark, for both ignore the fact that treponemal infections have been endemic in all the major races of mankind for as far back as we can look. It is possible that the venereal syphilis which played such havoc in sixteenth century Europe was due to a new strain of *Treponema* which had arisen in response to a changing environment, and may have originated anywhere. Besides venereal syphilis, other less virulent diseases caused by treponemas include yaws, pinta in central America, endemic syphilis (not transmitted venereally) in parts of Africa, etc. In a recent essay, T. A. Cockburn[3] presents an informed discussion on the origin of the treponematoses, and brings out many interesting facets. He points out that the treponemal infections form a group of closely related diseases, with curious clinical, epidemiological and distributional differences between the individual entities. The interrelations within the group have intrigued epidemiologists and bacteriologists for many years. Bacteriologically there are two schools of thought—those which regard the treponemal diseases as being caused by a more or less equivalent number of different species of *Treponema*, and those which consider that they are due to different variants or subspecies of the one species, *Treponema pallidum*. This is by no means an entirely semantic difference of opinion. Those who favour the unitary theory of the treponematoses accept the possibility that changes in environment might have led to the fairly rapid evolution of one form from another. Cockburn states that before the days of Columbus there were treponemal infections both in the Old World and in the New World of the Americas, and there is ample evidence that this was so. Pinta of central America is stated to have some very characteristic features, and Cockburn suggests that its failure to spread elsewhere may indicate that this strain of *Treponema* is particularly adapted to the Amerindian races and their environment. Bejel, also known as endemic or non-venereal syphilis, exists as a common skin lesion among people living in overcrowded conditions throughout the Middle East and in many parts of Africa, and still lingers in remote parts of the Balkan Peninsula. Hudson, whom we have already quoted, and who is one of the principal proponents of the unitary theory of treponemal diseases and a leading authority on the subject of endemic syphilis, states[4] that the number of people affected by endemic syphilis is probably far greater than the total affected by venereal syphilis. It is perhaps not widely known that as late as the eighteenth century a form of endemic syphilis, locally known as "sibbens", still occurred in the remote parts of Scotland. Yaws is, of course, still widespread in the tropics, and up till very recently sufferers from this treponemal condition were numbered in tens of millions. Endemic syphilis in its various forms is a disease of overcrowded conditions and poor personal hygiene, and is acquired mainly in childhood by close personal contact. An essential feature of all treponemal diseases is that, the parasite being a delicate organism, incapable of independent survival for even a short interval, they are transmitted only by intimate physical contact. Cockburn's thesis is somewhat as follows. As long as man lived under conditions in which his children were frequently huddled together in a state of nature, treponematosis was able to maintain itself as a relatively superficial infection. Partly for climatic reasons, such conditions continued much later in the tropics than in temperate regions. As the wearing of clothes became general, this interfered with such simple methods of transmission, and to survive the *Treponema* had to adjust itself to more specialized routes. A feature of the treponematoses is that a considerable degree of cross-immunity prevails. As improved living conditions led to the disappearance of non-venereal syphilis as a childhood disease, there emerged an adult population largely lacking in immunity to treponemal infection, and the stage was set for the emergence of venereal syphilis as a distinct entity. In the light of modern views on evolution it seems clear that, in the circumstances, the emergence of a strain of *Treponema* adapted to venereal transmission was virtually inevitable.

Cockburn also considers other problems raised by venereal syphilis, namely its distinctive proclivity to infect the fœtus in utero, and its tendency to cause lesions of the internal organs such as the central nervous system and aorta. Among the non-venereal treponematoses congenital infection appears to be almost unknown, and tertiary involvement of the aorta and the central nervous system appears to be equally rare. In venereal syphilis the tendency to congenital infection is fairly easily explained in an organism which has already adapted itself to infection of the genital tract. Under conditions in which repeated pregnancies were the rule, it is possible to see that repeated passage of the organism through

[1] "Toward the Conquest of Beriberi", by Robert R. Williams; 1961. Cambridge: Harvard University Press. 9¼" × 6", pp. 360. Price: 70s. 6d.

[2] "Non-Venereal Syphilis: A Sociological and Medical Study of Bejel". E. and S. Livingstone, Edinburgh and London, 1957.

[3] *Bull. Wld Hlth Org.*, 1961, 24: 221 (November 2).

[4] *Arch. intern. Med.*, 1961, 108: 1 (July).

successive fœtuses could result in the emergence of organotropic strains of the parasite. It may be argued that Cockburn's thesis is not new, and that in its essentials it has already been stated by Hudson. However, Cockburn explains it in evolutionary terms which greatly add to the force of the argument, and his paper is an interesting essay in the application of Darwinian principles to the study of the interrelationship of a very intriguing group of diseases.

SHORTER ABSTRACTS.

OPHTHALMOLOGY.

SIGNIFICANCE OF DIURNAL TENSION VARIATIONS IN NORMAL AND GLAUCOMATOUS EYES. S. M. Drance, *Arch. Ophthal.*, October, 1960.

THE author has carried out a study to evaluate the phasic diurnal intraocular pressure variations measured with the Shiøtz tonometer, in an unselected group of hospital patients who were not being treated for ocular disease. These served as a base line against which to compare the phasic variation of intraocular pressure found in untreated eyes with chronic simple glaucoma. The pressure was recorded using a 5·5 grammes weight every three hours from 6 a.m. to 10 p.m. Tonography was also carried out. The author studied 138 untreated glaucoma eyes in 72 patients. The patients were not put to bed and were encouraged to move about. In the normal eyes the mean diurnal variation was 3·7 mm. of mercury. A maximum pressure at 6 a.m. was shown by 42% of eyes, while between midday and 6 p.m. only 28% showed their highest intraocular pressure. The mean coefficient of outflow was 0·25 c.mm. per minute per millimetre of mercury. In the untreated chronic simple glaucoma series the mean phasic variation was 11 mm. of mercury. In 81 eyes with cupping and field changes the mean diurnal variation was 12 mm. of mercury, whereas in eyes without cupping or field changes the mean diurnal variation was 9·5 mm. of mercury. Peaks of intraocular pressure were found to occur outside usual office hours in 60% of patients, and during office hours in the remaining 40%. The author therefore concludes that borderline pressures recorded during office hours should not be lightly dismissed, for the intraocular pressures may be a good deal higher at the time of the peak of the diurnal tension variation.

INACTIVATION OF HERPES SIMPLEX VIRUS. T. W. Sery and F. P. Furgiuele, *Amer. J. Ophthal.*, January, 1961.

THE authors report on the use of various chemical compounds as antiviral agents against herpes simplex. They found that a number of agents are effective against extracellular herpes simplex virus but that the most suitable is silver nirate. They found that a 0·5% solution of silver nitrate was at least 100 times as potent as iodine as a virus inactivating agent. The authors suggest the use of 0·5% silver nitrate solution in the treatment of dendritic ulcer.

SCLERAL BUCKLING PROCEDURES. C. L. Schepens *et alii*, *Arch. Ophthal.*, December, 1960.

THE authors discuss scleral buckling procedures with the use of synthetic sutures and silicone implants. Silk sutures sometimes cause sterile abscesses or granulomas as they disintegrate; to overcome this, polyester fibre sutures which are better tolerated by the tissues have been substituted. The fibre used by the authors is "Mersilene". With this, the incidence of granuloma and sterile abscess is much lower than that observed with silk. For mattress sutures the authors use 0000 green braided polyester fibre on number 82 Grieshaber needles. The circling suture is 00 braided white polyester fibre. The silicone implants used are of various shapes and sizes. Straight silicone implants may be grooved or ungrooved and are 125 mm. long. At operation they are cut to required size and the remainder kept, since silicone rubber can be reautoclaved. Ungrooved rectangular sections are available in various sizes and these are used in trap-door procedures. Grooved sections are the most commonly used; the narrower of the two grooved forms is 4 mm. wide on the grooved side, and when embedded in a resection with a circling tube in its groove it will engage a width of 6 mm. on its inner surface. The wider tube requires a scleral bed of 9·5 mm. The authors describe their techniques for trap-door procedures with silicone, circling tube over grooved silicone, and circling tube over curved silicone. The last is used where there are giant breaks or multiple breaks which cover an extensive area of the retina. The authors have found the use of silicone and circling tube far superior to the use of circling tube alone.

PENICILLIN-STREPTOMYCIN-GELATIN DISCS IN THE TREATMENT OF HYPOPYON ULCERS. A. D. Grover, *Brit. J. Ophthal.*, January, 1961.

THE author has compared the use of gelatin discs containing penicillin and streptomycin with subconjunctival injections of these drugs in the treatment of hypopyon ulcers. In one group of patients the gelatin discs were applied locally three times daily and in the other group subconjunctival injections were given on alternate days. In addition both groups were given hot fomentations twice daily and 1% atropine ointment three times daily. If there was no improvement in 48 hours the therapy was considered to be a failure. Treatment was continued until the ulcer was no longer stained with fluorescein. The author concludes that the results obtained with the gelatin discs were as good or even slightly better than those obtained by subconjunctival injections. The discs were well tolerated by all patients.

THE SIGNIFICANCE OF SPOTTING OF THE IRIS IN MONGOLOIDS. D. D. Donaldson, *Arch. Ophthal.*, January, 1961.

STEREOCAMERA PHOTOGRAPHS of the irides of 180 mongoloids were studied and compared with those from 146 normal individuals, aged from five to 60 years. Twelve infants from three hours to five days old were photographed and were used as controls. The photographs were analysed as to the incidence of spots in relationship to the colour of the eyes, number of spots per eye, portion of iris in which spots occurred, distinctness of the spots and hypoplasia of the iris. The incidence of spots was 85% in mongoloids, and 24% in normal subjects. In mongoloids the spots were more often in the midzone and in normal subjects in the periphery. The spots in mongoloids were more distinct. There is a marked degree of thinning or hypoplasia of the peripheral portion of the iris in mongoloids. There is no correlation between the iris spotting and the age or the I.Q. of the mongoloid. The author concludes that spotting of the iris with hypoplasia can be used in the diagnosis of mongolism.

METHODS FOR SEPARATION OF LIDS IN CATARACT SURGERY. P. V. Fechner, *Amer. J. Ophthal.*, January, 1961.

THE methods used in separating the lids during cataract surgery are reviewed. The purposes of the lid speculum are to give retraction to the lids, not to impair the work of the surgeon, to be effective without manual help, not to exert pressure on the eye, to permit the lifting of the lids from the eye, to permit the lessening of the width of the palpebral aperture, and to permit these last two functions to be carried out by the assistant without hindering the surgeon. All methods, including the various types of speculum, are examined in the light of these criteria. The author describes a modification of the simple speculum which he believes fulfils these requirements.

GLAUCOMA IN THE YOUNGER AGE GROUPS. E. S. Perkins, *Arch. Ophthal.*, December, 1960.

THE records of over 3000 patients from two glaucoma clinics were studied, cases of buphthalmos being excluded. It was found that about 35% of cases of closed angle glaucoma occur before the age of 50 years and are almost equally divided between the two sexes; of the 20% of cases of open angle glaucoma commencing before this age there is a preponderance of males in the ratio 2:1. The sex ratio in the older age groups is 1:1. It is possible that some of these cases in the younger age group are pigmentary glaucomas. Analysis of this group showed that pigmentation increased with age but that there was a distinct peak in the 30 to 40 years age group. In view of the reported predominance of myopia in pigmentary glaucoma the refractive state in this series was investigated. It was found that over 37% of patients had over one dioptre of myopia and more than half of these had over four dioptres. Of the males, 40% were myopic as compared with 31% of the females. In many of the cases of pigmentary glaucoma haloes were reported, an uncommon symptom in open angle glaucoma. It has also been reported that some cases of

pigmentary glaucoma have a positive mydriatic test in spite of the presence of an open angle with the pupil dilated. The author concludes that pigmentary glaucoma is part of a larger syndrome consisting of a developmental defect in the outflow channels, found most commonly in myopic males, and that the pigmentation is not the primary cause of the glaucoma. Suspicion of glaucoma should be aroused by patients in the 30 to 50 years age group who are myopic and show pigment deposits on the posterior surface of the cornea. A history of haloes or attacks of blurred vision should suggest attacks of raised tension even though the appearance of the eye and the angle are unlike those of closed angle glaucoma.

OTO-RHINO-LARYNGOLOGY.

POSITIONAL OTITIS MEDIA. R. B. Duncan, *Arch. Otolaryng.*, 1960, 72: 454-463 (October).

THE author put forward a concept relating to the occurrence of otitis media in infants who are bottle-fed. Reflux of food may occur into the post-nasal space and nose when the infant is fed in the supine or horizontal position. He states that there are other factors such as the state of the nose, teething, condition of the bedroom, the month of birth and the weather conditions. He states that for bottle-fed babies feeding in an upright position should be the rule for all young babies up to the age of three months, for all babies or infants in hospital, for all premature infants, for babies whose nose is blocked by allergic reactions, or by bacterial or virus infection, and for older babies who have had positional otitis media.

MALIGNANT MELANOMA OF THE NOSE AND PARANASAL SINUSES AND JUVENILE MELANOMA OF THE NOSE. J. Ravid and J. Esteves, *Arch. Otolaryng.*, 1960, 72: 431-444 (October).

THE authors review the world literature relating to malignant melanoma of the nose, and report two cases, one of a malignant melanoma and the other of a benign juvenile melanoma. They point out the apparent variety of these tumours as evidenced by the literature reports, and stress the poor prognosis (e.g., Pock and Englem report a 9% five-year survival rate for these tumours in the oro-nasal region). Local recurrence and adjacent spread is the usual terminal event. Early diagnosis with radical surgery is the only way to attempt any sort of treatment in these cases. The authors describe the symptomatology, location, and course and duration of the disease usually found in cases of malignant melanoma of the nose. It is doubtful if these tumours ever occur primarily in the accessory nasal sinuses.

PRE-EPIDERMOSIS. A. TUMARKIN, *J. Laryng.*, 1961, 75: 487-500 (May).

THE author discusses cholesteatoma. He states the differing opinions regarding its ætiology and its histology, and sets out a new conception to allow easier comprehension of the true nature of this condition. The following two important factors are discussed: (i) Is it possible to demonstrate true stratified epithelium? To this the author answers in the affirmative. (ii) Is the presence of cholesterin crystals an essential feature? The author states that these crystals have nothing whatever to do with cholesteatoma. To distinguish two different entities, the author suggests new nomenclature to do away with the title cholesteatoma. He suggests cholesterol granuloma (cholesterin crystals, granulation tissue and giant cells) seen in exudative otitis media, and also epidermosis typified by true epidermis within the tympano-mastoid cavity. The theories of origin are discussed and the surgical method of treatment for each type is suggested. The author points out that when both conditions are present, no final suggestion is forthcoming for the correct surgical procedure.

BLOODLESS OPERATING FIELD IN MIDDLE EAR SURGERY. F. Holmes, *J. Laryng.*, 1961, 75: 248-258 (March).

THE author discusses the problems of providing a bloodless operating field for reconstructive procedures on the middle ear, on the basis of a review of 138 cases of hypotension induced with hexamethoxium bromide. The following factors provide problems in this operative field. (i) Blood has a tendency to accumulate in the middle-ear cavity. (ii) Chronic or subacute infection and hyperæmia are frequently present. (iii) The smallness of the structures encountered requires a relatively less amount of blood to obscure them from view. Much of this type of surgery is performed on otherwise young and healthy adults, who are considered to be particularly resistant to ganglionic blockade. The clinical material is divided into three groups, of approximately equal numbers, according to the method of general anæsthesia employed. The choice of anæsthetic agent had an important influence on the degree of wound ischæmia obtained. Other important factors in this respect were the age of the subject, the pathological process and the individual response to postural change. Tachycardia appeared to be the most constant factor whenever bleeding was troublesome during operation.

THE NEW MEATAL PEDICLE GRAFT FOR RESTORATION OF THE EARDRUM. H. L. Bell, *Laryngoscope*, 1961, 71: 319-328 (March).

THE author gives a general statement of variations in technique with some historical review, and then describes a method adopted by him and used in some 100 cases. In all cases an endaural incision is employed. He points out that this is necessary because it is almost impossible to prepare a pedicle flap large enough without the endaural incision. He also emphasizes the necessity to inspect the middle-ear cavity and/or attic region for cholesteatoma through an osteotomy incision in the attic wall at the postero-superior annular rim. This method can be used in drum deficiencies of any size. A description of the method is given. The advantages of this technique are listed, as follows: (i) The incidence of "take" is much higher than that of free graft. (ii) Blood supply to the graft is assured. (iii) There is very little desquamation of the graft after "take". (iv) The graft is easy to prepare. (v) There is greater exposure of the drum area. (vi) It is a step-by-step procedure, eliminating guess work and can be used in all types of tympanoplasties.

ADENOCARCINOMA OF THE MIDDLE EAR. I. S. Jaffee and R. S. Page, *Laryngoscope*, 1961, 71: 392-395 (April).

THE authors state that this is a rare condition. The case which they report is only the seventh in the literature. Whereas malignant disease of the middle ear is usually squamous carcinoma and usually follows long-standing otorrhœa, adenocarcinoma, sarcoma and chemodectoma may present without discharge. Other signs suggestive of middle-ear malignant disease include increasing pain, bleeding, visible growth, decreasing hearing, facial palsy, vertigo, tinnitus and mastoid tenderness. The authors present details of their case, which presented with right facial asymmetry of two or three days' duration. A radical mastoidectomy was performed, and the "granulation tissue" was reported to have foci of adenocarcinoma. The suggestion of radical surgery of the petrous bone was refused and X-ray therapy was instituted. The authors state the prognosis of the disease is poor. It would seem that any chance of survival lies in the field of radical surgery of the petrous pyramid, mastoid and squamosa.

DIRECTIONAL PREPONDERANCE IN TEMPORAL LOBE DISEASE. L. E. Sandberg and K. Zilstorff-Pedersen, *Arch. Otolaryng.*, 1961, 73: 139-144 (February).

THE authors present a report of the investigation of 35 cases of temporal-lobe lesions, all proved at operation, and set out to confirm the finding of Hallpike *et alii* that in cases of temporal lobe lesions, directional preponderance to the affected side occurs in the differential caloric test. But whereas Hallpike *et alii* stated that the directional preponderance occurred when the lesion was in the posterior part of the temporal lobe, the present authors found this directional preponderance in six of a total of 13 cases in which only the anterior part of the temporal lobe was affected. Also in five of the 11 cases in which both the anterior and posterior parts of the temporal lobe were affected, this directional preponderance was present. In all cases in which it was present, the preponderance was to the side of the lesion. In most cases neuro-ophthalmic examination produced abnormal findings in most cases. There were no auditory losses, and none of the patients had complained of tinnitus. Nineteen had suffered from "uncharacteristic" attacks of dizziness for varying periods of time. Electroencephalographic examination also produced abnormal findings in all but two cases. The authors state that the normal electroencephalogram, the neuro-ophthalmological findings and the caloric test militate against temporal lobe lesion.

Brush Up Your Medicine.

THE "ACUTE ABDOMEN".[1]

EVERY medical practitioner knows that if he fails to diagnose a chronic disease on the patient's history, he will seldom do so on clinical examination. Acute abdominal pain, on the other hand, is so urgent a matter, and striking signs are so often present, that to take a careful history may seem pedantic. But if he remembers, first, that different acute lesions may give similar signs (and, after all, the end result of many of them is the same—namely, general peritonitis), and secondly, that pain from different organs may be referred to the same spot on the body surface, he will soon be persuaded to ask questions first, not afterwards.

Anatomical Origin of Abdominal Pain.

The anatomical origin of abdominal pain can be determined from its referral. The most important question undoubtedly concerns the pain. The medical attendant can decide in what abdominal (or other) structure the pain arises only if he understands something of the phenomenon of referral.

Abdominal pain is deep pain and is always referred to the skin. The patient points to his skin; he cannot see his viscera or his peritoneum. Admittedly, pain due to irritation of the anterior abdominal peritoneum does not appear to be referred, but seems to be "right on the spot". This is only because the dermatomes, or skin areas served by the same cord segments, directly overlie the corresponding peritoneal area. It is only when the diaphragmatic parietal peritoneum is inflamed that referral becomes obvious, because the corresponding dermatome happens to be distant—that is, at the shoulder-tip.

Apart from the site at which it is felt, the quality of the referred pain depends on its site of origin. When the anterior parietal peritoneum is involved in acute visceral disease, the referred pain is more sharply localized and tenderness and rigidity are more marked, simply because there is a denser concentration of pain fibres here in the peritoneum than in the viscera themselves. Tenderness and rigidity, in fact, are rarely gross or localized unless the anterior parietal peritoneum is directly irritated. In colic, for instance, which is purely visceral in origin, tenderness and rigidity are mild compared with the severity of the pain.

Pain arising in a viscus or in the peritoneum is constantly and always referred to the same place. Ureteric pain is always unilateral and is always felt in the skin areas supplied by the tenth thoracic to the first lumbar segments. Gall-bladder pain is always felt over the seventh to ninth thoracic dermatomes. However, this constant referral of pain from deep structures to the same dermatomes is less helpful than it sounds, because several organs may share the same dermatomes. Duodenal pain is referred to the same site as biliary pain. Pain from the heart may be felt in the epigastrium. All bowel colic is central wherever the causative lesion is, from jejunum to sigmoid.

The Pathological Basis of Abdominal Pain.

The pathological basis of abdominal pain can be determined from the nature of the pain. The various pathological states underlying the "acute abdomen" produce characteristic pain syndromes. Considered with the localizing features of referral already described, identification of such a syndrome enables a specific diagnosis to be made—that is, not merely which organ, but what disease.

In fact, it is possible to divide all "acute abdomens" into colics, inflammations, perforations and strangulations, though there is some overlap. In particular, colic may be followed by inflammation (for example, impaction of a stone in the cystic duct may lead to acute cholecystitis) and inflammation (for example appendicitis) may cause perforation. Acute pancreatitis, indeed, behaves like a perforation, and should be considered as one.

Colic.

A colic begins abruptly but mildly, becomes severe, and then wanes; it is, after all, related to intermittent smooth-muscle contraction in a distended organ. At its height the patient is restless, cannot keep still, moves about to get relief, and may apply heat to the abdominal wall dermatome as a counter-irritant. The more severe a colic is, the further it radiates—but it radiates, as we have seen, in a constant way, along the corresponding dermatomes of the organ.

Such a pain may last for seconds or hours. Its duration depends on the organ, another useful diagnostic point. Intestinal colic lasts a few seconds or minutes, ureteric colic half an hour, biliary colic one or more hours. In the diagnosis of mechanical intestinal obstruction, it is safe to say that the most important fact to establish is the presence of intestinal colic. An intermittent brief central pain, making the patient restless, and associated each time with a burst of loud bowel sounds, is intestinal colic; this always precedes vomiting, abdominal distension and constipation in small-bowel obstruction, though constipation (and sometimes distension) usually precedes colic in colon obstruction.

In biliary colic, of course, jaundice appearing in 12 hours means that the stone is in the common duct and not the cystic duct. It is, however, possible to have common duct colic without jaundice, particularly after cholecystectomy, when the common duct may have become inured to repeated intermittent dilatation.

It should be remembered that the temperature and pulse are normal in colic; there is no reason why they should be otherwise. In fact, owing to vagal stimulation by visceral distension, the pulse may be reflexly slowed.

Lastly, local signs are few, because the anterior parietal peritoneum is not irritated; even if the colic is severe, local tenderness and rigidity are disproportionately slight. However, it should be remembered that gross distension of viscera lowers their threshold for pain, so that, for instance, grossly distended bowel in mechanical or paralytic obstruction may be tender even though there is no strangulation.

Inflammation.

Just as inflammation is a continuous process, so is its pain, which may begin gradually or abruptly—perhaps as a colic in appendicitis, cholecystitis, calculous pyelonephritis; but, however it begins, it gradually grows worse, is sometimes throbbing in character, and spreads wherever the inflammation spreads. Movement is avoided because it makes the pain worse. The patient feels hot or cold, and the rise in temperature and pulse rate depends roughly on the size of the inflamed organ. Thus, the appendix is small and the temperature may be hardly raised in acute appendicitis; a sudden rise of temperature usually means perforation and peritonitis. If the temperature is high early, the diagnosis is unlikely to be appendicitis, but may be inflammation of a larger organ—for example, gall-bladder or Fallopian tubes.

Local tenderness, rebound tenderness, crossed tenderness and crossed rebound tenderness and rigidity are pronounced. These signs are closely related to inflammation of the overlying anterior abdominal peritoneum, and will not be pronounced if the gall-bladder is hidden under the liver edge or if the appendix is retro-caecal or pelvic. On the other hand, they are most useful because of the correspondence of the dermatomes with the underlying peritoneum. Thus, cholecystitis cannot produce local tenderness and rigidity confined to the left hypochondrium, while appendicitis cannot produce tenderness in the left renal angle.

As a corollary, it follows that an acutely inflamed organ in contact with the anterior parietal peritoneum is rarely palpable in the early stages, because of the overlying muscle rigidity. A tense gall-bladder palpable immediately

[1] Read during the General Practitioner Refresher Course, St. Vincent's Hospital, Melbourne, September, 1960.

after a biliary colic is due to mucocele, not to empyema. It is only when the inflamed organ becomes wrapped in omentum that the parietal peritoneal pain abates; the peritoneum is no longer directly irritated, the rigidity passes off, and a mass (not the organ, but the organ wrapped in omentum) becomes palpable for the first time. Even though the affected organ is swollen, distended, engorged and indurated with inflammation, a palpable mass is not an early sign in acute inflammation of abdominal viscera. Needless to say, such a mass, when eventually felt, is not necessarily an abscess. It may become one, but it is more likely to subside with treatment than to suppurate.

Perforations.

Perforations are usually unmistakable unless existing peritoneal adhesions localize them, or unless perforation occurs into the lesser sac only.

There may have been some sort of pain immediately beforehand, but this suddenly and dramatically becomes severe and quickly spreads over the abdomen. When inflammatory lesions perforate, there has invariably been some preexisting pain at the site of inflammation—in the right iliac fossa in appendicitis, in the left iliac fossa in diverticulitis—and this makes diagnosis relatively easy. However, peptic ulcer perforation, acute pancreatitis, foreign-body perforation of the gut or local perforation at the site of a colonic carcinoma may occur without warning. In these cases it is enormously important in diagnosis to know where the pain began, because it remains momentarily local before spreading and gives a clue to the organ affected. Fortunately, this first pain is usually the worst pain, and pain usually remains more severe near the site of perforation than elsewhere.

The pain remains constantly severe until peritoneal effusion is gross; then it abates for a few hours (*intermission trompeuse*); then it recurs as peritonitis becomes established. In the first few hours the patient cannot move, breathing hurts, even vomiting is avoided. The temperature falls in perforated ulcer, pancreatitis and carcinoma, but may quickly rise if the peritoneal cavity is flooded with pus, as in perforation in appendicitis, diverticulitis or cholecystitis. The pulse rate rises soon, though the blood pressure is normal (except in severe pancreatitis and perforated peptic ulcer in the aged). Widespread rigidity is present and is even more striking than (and may mask) the widespread tenderness, present in all four corners of the abdomen, and is appreciable rectally. The abdomen is ominously silent. There may, in perforation of stomach, duodenum and colon, be evidence of free gas under the diaphragm (diminished liver dullness to percussion) or of free fluid in the peritoneal cavity.

Sudden severe intraperitoneal hæmorrhage is a kind of perforation, but the patient is pale and really, not merely apparently, shocked—that is, the blood pressure is low.

Strangulation.

Strangulation of external herniæ should not be missed; such a hernia, remember, will be tense and irreducible, but it may be neither painful nor tender. Internal strangulations also have definite characteristics. The main distinguishing feature is the effect of ischæmia. Colic, usually present, is more severe and more frequent, though often absent in mesenteric vascular occlusion. More important, there is a constant pain, persisting until the organ and its nerves are dead, often localized at the site of strangulation, where there is usually local tenderness. If a large organ is strangulated, pallor and shock are present without external blood loss, internal bleeding without the local signs of intraperitoneal hæmorrhage—an almost pathognomonic picture in mesenteric vascular occlusion.

In strangulation—and here is a striking difference from inflammation—the tense, engorged organ, whether it is a twisted gall-bladder or ovarian cyst or a strangulated loop of bowel, is often palpable because there is less overlying rigidity. A pathognomonic triad of signs of internal strangulation is shock, local tenderness, palpable mass.

Conclusion.

I have attempted to recall for you the bases of acute abdominal pain, and to illustrate the various pain syndromes by reference to their commoner examples. The emphasis has been on clinical diagnosis, and I make no apology for not discussing special investigations or details of surgical treatment, which is fairly standardized. I have not discussed medical or gynæcological lesions, which must not be forgotten.

I should like to emphasize finally that 20% of "acute abdomens" are not susceptible of accurate diagnosis. In these cases, when extraabdominal disease has been excluded, early laparotomy is necessary. When severe undiagnosed pain persists, or when it is at once obvious that some intraperitoneal catastrophe has occurred, more lives will be saved by operation than by procrastination.

Peter Ryan, M.S., F.R.C.S., F.R.A.C.S.,
Melbourne.

Out of the Past.

HOSPITAL FOR SICK CHILDREN, SYDNEY.[1]

[From the *Australasian Medical Gazette*, April 20, 1903.]

In their 23rd annual report the board stated that 560 patients were admitted during the year to the general hospital and there were 44 remaining from the previous year. Of these 394 were discharged cured, 70 relieved, 35 unrelieved, and 63 died. There were 177 admitted to the diphtheria hospital, and of them 143 were cured and 23 died. The out-patients numbered 3525. Compared with the previous year there was an increase of 68 patients treated in the general hospital. The death rate was 10·4 per cent., as against 11·1 per cent. last year. In the diphtheria branch there was a decrease of 14, while the death rate was 12·02 per cent., as against 18·8 per cent. in the previous year. The out-patients' department had been erected in Valentine-street, off George-street, and was now in full work, the number of children treated in the more commodious and centrally situated premises during the short time they had been opened for the reception of patients showing already a very large increase. It had also been possible to carry out the establishment of a convalescent home in connection with the hospital. The board of the Carrington Centennial Hospital Home for Convalescents offered to let on very favourable terms a cottage known as Grasmere, situated at Camden, and it was decided to accept the lease. The cottage had accommodation for 14 cots, and was at present in full occupation. During the past many of the children leaving the hospital had been cared for by the Walker Convalescent Hospital. The board had been unable to take any further steps towards building a new general hospital. The necessity for a new building was pressing, the present premises being absolutely inadequate and unsuitable for the work which should be done by a children's hospital in Sydney. The institution was again indebted for the success which had attended the work being done during the year to the skill and unremitting devotion of the honorary staff.

Correspondence.

THE DANGERS OF SOME ANTIDEPRESSANT DRUGS.

Sir: I feel I should draw attention to the dangers attached to some of the newer antidepressant drugs (tranylcypromine in particular) following a fatal case of my own. Paradoxical rises in blood pressure with nausea and vomiting have been reported with this drug by Dr.

[1] From the original in the Mitchell Library, Sydney.

John Clark[1], who was sufficiently disturbed to discontinue a clinical trial.

My own patient was a depressed woman of 54, who received tranylcypromine 10 mg. twice daily for a period of seven days, along with two electroconvulsive treatments. She was also receiving "Librium", 10 mg. four times a day. Her depression responded very well, and three days after her second electroconvulsive treatment she was quite well, and I discussed going home with her. Her only complaint at this time was that she felt slightly drowsy at times. To combat this, I prescribed amphetamine sulphate, and she received one tablet only of 5 mg. mid-morning. Soon after this she complained of intense headache, which was followed by vomiting, and she then collapsed. I saw her about two hours after taking the amphetamine, when she had a left-sided flaccid paralysis, which later became spastic, and it was obvious that she had suffered a cerebral hæmorrhage. Her condition gradually deteriorated, and she died in coma three days later. Post-mortem was not carried out. Her initial blood pressure was 150/90. When examined after the hæmorrhage, although appearing shocked, it was 170/90. There was no evidence of arteriosclerosis on routine examination at the commencement of her treatment—radial artery was not unduly hardened and fundal arteries appeared normal.

It seems clear that the single dose of amphetamine precipitated the sudden rise in blood pressure in a person already sensitized by tranylcypromine and that this proved too much for a weakened cerebral artery. I would suggest that caution be exercised with such drugs in any patient who shows any tendency to arteriosclerosis, and that prompt administration of hypotensives be given should a crisis similar to the ones described occur.

Yours, etc.,

260 St. George's Terrace, Perth.
PAUL ZECK.

September 14, 1961.

DRINKING, THEN DRIVING DANGEROUSLY.

SIR: I wish to support the articles by Dr. J. H. W. Birrell, "Driving under the Influence of Intoxicating Liquor in Victoria", and Dr. G. S. Hayes, "The Drinking Driver" (MED. J. AUST., September 9, 1961). Three essentials are concerned: (i) apprehension of the driver by the police; (ii) medical examination of the accused by a doctor, supported by biochemical aids; (iii) trial before a magistrate, or judge and jury.

Apprehension of the Driver by the Police.

A policeman is generally recruited as a young man, then following basic training, is supposed to be mature and experienced enough to take correct and quick action on his own initiative. He must assess the driver's capabilities, and apprehend when necessary. At trial, sometimes months or many months later, his evidence is supposed to be exact and pertinent. We must be aware of police problems because, should a policeman be indefinite, he has to withstand severe cross examination, often ridicule, by a thrusting learned counsel.

Medical Examination of the Accused by a Doctor, supported by Biochemical Aids.

Recently, as a country general practitioner, I examined, when requested, any driver charged with driving under the influence, at any hour, day or night, supported by blood alcohol tests. My conclusions are as follows. (*a*) Venesection apparatus should be available to all police stations, prepared and sterilized at local hospitals. (*b*) Notwithstanding biochemical aids, a physical examination is always necessary; preferably two should be performed, the first on arrest, the second on the day following or prior to trial, for comparison. Determinant reasons are as follows.

1. The demeanour of the accused is always noted by the prosecution at the trial, therefore the medical examiner should record physical state, derangement of clothing, slurred speech, gait, mental agility, and also the history of the incident given by the accused, the accident, the alcohol consumed. The accused's character should be assessed.

2. Coincidental illness should be sought. Drugs may have been taken. If a psychiatric condition is present, the patient may have taken stimulants or sedatives. Patients often have to take two or three types of drug at the one time. The question arises whether the patient is doped when alcohol is superadded. Elderly people may be taking hypotensives or vasodilators; if they are taking diuretics, alcohol may further debilitate them. In allergy, antihistamine sedative action may be enhanced by alcohol. Physical debility may be a factor, as in ulcer patients, in inadequate nutrition, and in anxiety.

3. A check should be made of the cardio-vascular system, the respiratory system, the nervous system, and the patient's general fitness.

4. An examination is also necessary to assess trauma and shock. Some drivers may have to crawl up a gully, the car smashed, one passenger killed, another to die later.

However, I admit that physical examination may not always be adequate, as one case history will show. A rural labourer, aged 19 years, had a blood alcohol content of 215 mg. per 100 ml. (13·5 seven-ounce beer middies or 13·5 ounces of spirit in the blood when the test specimen was taken at 3 a.m.). He could write legibly and stand steady and erect, and his coordination was excellent. He had not eaten since breakfast at 7 a.m. on the preceding morning. He stated that the alcohol consumed was only three seven-ounce middies at 6.30 p.m. and two banana cocktails at 10.30 p.m. His blood pressure was 90/65 mm. of mercury, and his pulse after five press-ups was 132. Five minutes later it was 120. His mental arithmetic (addition, subtraction and multiplication of money amounts) was very good, notwithstanding limited formal education. The blood test clinched the diagnosis.

Trial before a Magistrate, or Judge and Jury.

Should there be a twenty-four-hour magistrate service for pre-assessment of drivers so charged? British justice is fair; an accused must understand the reasons for his trial, and have available adequate defence facilities.

As medical graduates and undergraduates, we must be aware of the effects of alcohol, with or without drugs. In court, if granted expert witness status, we need to be expertly informed on biochemical aids and the latest procedures, to help the court reach a decision. Our duty is to understand court procedure, the requirements of medical evidence, the role and purpose of the magistrate, the higher role of the judge and jury, the function of the police.

Sound colour films, with trained projectionists, should be available to record the accused's demeanour on arrest and during medical examination.

Comment.

Conflicting evidence for and against the accused would by these means be kept to a minimum, as would our road casualty list, now a national emergency. Note particularly, recent Press reports mentioning our post-graduate studies being advanced by television. Finally, we owe a duty to ourselves and fellow citizens so accused to medically examine them at their request or at the request of officers of the law. Any one of us, whilst driving, may one day, owing to illness, injury or shock, with or without alcohol or drugs, require a fellow graduate's skilled aid. We should always advocate, "no drinking when driving".

Yours, etc.,

1 Eaton Avenue, Normanhurst, N.S.W.
DAVID HODGKINSON.

September 18, 1961.

FLUORIDATION OF PUBLIC WATER SUPPLIES.

SIR: Possible fluoridation risks include:

1. Increased incidences of mongolism (recently suspected), spondylosis (proven in gross cases), goitre and hypothyroidism (documented for South Africa by Professor Steyn's monograph, which contradicts your statement of September 16 editorial that "The only demonstrable ill effect is the mottling of teeth which occurs when fluoride is present in high concentrations").

2. Abnormal cumulation in certain nephroses.

[1] *Lancet*, 1961, 1: 618.

3. Abnormal absorption in certain mineral environments. Whereas the highly soluble sodium salt is the usual artificial additive, natural fluorides occur mainly as calcium fluoride.

4. Increased radio-active strontium deposition in children (Kerwin[1]).

These objections have not been seriously refuted. I cannot therefore justify your statement "nothing has happened to justify the warnings of the alarmists". How can you know? It would be as true for the Kremlin to claim "nothing has happened to justify the alarmists" of the United Nations Scientific Committee on Radiation, 1958, who claimed there will be 400 to 2000 deaths yearly from leukæmia and 70 to 900 from bone cancer from tests to that date. These figures do not allow for "hot spots" in bone later described by Swedish workers, leading to 10 times higher doses, and of course ignore completely congenital dysgeneses and non-bone cancers, including children's thyroid cancers (Rooney and Powell[2], Campbell *et alii*[3]).

The water engineers of New York who claim fluoride content can be maintained "within 5% of the desired level" evidently had much more expensive equipment than that available here. The figures I have read for analyses taken from taps at random from a city supply varied much from this figure.

You dismiss the value of the ante-natal fluoride tablet. You ignore the baby-clinic and school tablet, which could be provided more cheaply than fluoridation. How could such dosage be more haphazard than that which would allow a child in Cairns to absorb the fluoride from a gallon of water a day (some foods will contain a higher concentration than the water after boiling), while another child is raised on milk, fruit juice or industrially-defluoridated soft drink? Many industries use costly defluoridating plants.

More good could be done to our future generation, our dentists and our primary industries by giving kindergarteners an apple a day, than by fluoridation, which seeks to patch up the defects of civilized eating and provide a cheap means of disposal for a toxic by-product of the aluminium industry—sodium fluoride, at present a costly embarrassment to aluminium refineries.

Yours, etc.,

D. EVERINGHAM.

P.O. Box 328,
Rockhampton,
Queensland.

September 18, 1961.

[As Dr. Everingham questions the opinion expressed in our editorial article, we feel constrained to state that the "possible risks" listed by Dr. Everingham are precisely the kind of statements which we had in mind when we wrote "nothing has happened to justify the warnings of the alarmists". The subject has been repeatedly and thoroughly ventilated, but informed medical and dental opinion remains overwhelmingly to the effect that there is no acceptable evidence that fluoridated water is any danger to health, even when the fluoride content is greatly in excess of recommended levels. We hope that other correspondents will express their views.—EDITOR.]

TIME FOR REVISION OF THE McNAUGHTEN RULES.[4]

SIR: There is mounting evidence that the McNaughten Rules have been in need of a sensible revision for a long time. It becomes more and more apparent, not only to those of us who are called upon to give opinion in cases of insanity as a defence in criminal law. The concept of guilt and criminal responsibility has been studied for a long time. In the light, however, of the new developments and the recent progress in psychiatry, it is obsolete to have to give an opinion in the frame of the McNaughten Rules.

It may be of value to be reminded that the McNaughten Rules have been in existence from 1843. McNaughten shot Mr. Edward Drummond, mistakenly taking him for Sir Robert Peel, to whom Drummond was the secretary. It was the first case of a defence of insanity. The House of Lords asked judges for an opinion regarding this matter, and their reply has become known as the McNaughten Rules. They require from psychiatrists replies to the following questions: (i) whether at the time of committing the act the accused was labouring under such defect of reason from disease of mind as not to know the nature and quality of the act he was doing; (ii) if he did know what he was doing, whether he did not know that it was wrong.

Since then a number of committees have been appointed to investigate the problem of insanity and criminal responsibility. One of such was a committee of the Royal Medico-Psychological Association, when suggestions for amendments were made which were not accepted by the legal authorities then. It would be of interest to quote them in short. The Royal Medico-Psychological Society recommended that the legal responsibility expressed in the McNaughten Rules should be abrogated in every trial in which a prisoner's mental condition is at issue, the judges should direct the jury to answer the following questions: (*a*) Did the prisoner commit the act alleged? (*b*) If he did, was he at the time insane? (*c*) If he was insane, has it nevertheless been proved to the satisfaction of the jury that his crime was unrelated to his mental disorder?

A number of legal authorities (e.g., Stephens, in the "History of Criminal Law of England") commented on the McNaughten Rules, suggesting that they should be widened to include diminished responsibility (recently raised in the daily newspapers after comments of a Supreme Court judge in the Central Criminal Court). Also the problems of an irresistible and uncontrollable impulse were discussed. These are serious matters, mostly legal, but they have a great significance to the medical profession. However, very little has been done to revise the Rules here in Australia to date.

To the unbiased and not prejudiced, it will become clear that very rarely is an accused "sufficiently mentally ill" (or bluntly "mad enough") to fit to those rules. We can have, e.g., a paranoid schizophrenic who knew the nature and quality of the homicide which he may have committed, and he probably knew it was wrong. And so he is "legally sane". On clinical evidence, as medical practitioners, we are not in a position to reply whether a patient knows that what he was doing was wrong or right. This is a matter for the court to decide.

There is a need for a modern Pinnell to break the chains of this obsolete law which helps to incarcerate a mentally ill person because he does not fit the requirements of McNaughten Rules. I feel that there are enough valid reasons for us here not to have only to follow others in attempts to bring more light into this obscure problem. It is time that we, in this important field, did something not sufficiently attended to by others. It does not mean that the criminal responsibility and liability to punishment was not already modified in Denmark and Sweden, as I have recently seen there. In England some modifications of the McNaughten Rules were formulated in so-called "diminished responsibility", and in the United States of America in six out of 50 States new Rules, the "Durham Rules", are now valid.

One of the co-authors of the Durham Rules, Judge Bazelon of the Supreme Court in Washington, D.C., told me about two months ago during my visit there of the basic reason for the formulation of those new rules from the legal point of view. The Durham Rules, on the basis of psychiatric opinion, have the jury determine (i) whether the defendant was sane or insane at the time of the alleged crime, and if he was insane, (ii) whether the harmful act was the product of his insanity.

Some of us may feel that the Durham Rules go too far, even if it was said that they are "a meeting ground for lawyers and psychiatrists; but it is time that we seriously sat down and prepared amendments to the McNaughten Rules which may replace the mediæval way of thinking in dealing with those matters, and that we adopt a new concept of guilt and criminal responsibility.

In a recent issue of the *British Medical Journal* it is reported in the editorial article a debate in the House of Commons, on crimes of violence, a plea by two speakers that "the Courts make more use of medical evidence so that the wicked go to prison and the sick to hospital".

I think it would be of interest to all of your readers, Sir, to know that a meeting is being organized by the undersigned to bring about the long overdue modification to the McNaughten Rules here. The Attorney-General, the President of the Medico-Legal Society, the Senior Crown Prosecutor, the Public Defender and others will take part in this meeting. The problem is vital to all, not only to us in the medical profession, but also to lawyers and to society at large.

[1] *Dental Digest*, February, 1958.
[2] *J. Amer. med. Ass.*, 1959, 169:1.
[3] *Amer. J. publ. Hlth*, 1959, February; abstracted in MED. J. AUST., 1959, 2:192 (August 8).
[4] Sometimes spelt M'Naghten.

I will be grateful to receive suggestions of amendments from those interested.

Yours, etc.,

"Wyoming",
175 Macquarie Street,
Sydney.
September 16, 1961.

OSCAR R. SCHMALZBACH.

Bibliography.

WILLIAMS, G. L. (1953), "Criminal Law", Stevens, London: 86.
SMITH, S., and SIMPSON, K. (1956), "Taylor's Principles and Practice of Medical Jurisprudence", Churchill, London: 575.
PERKINS, R. M. (1957), "Perkins on Criminal Law", Foundation Press, Brooklyn: 763.
British Medical Journal, 1961, 2: 436 (August 12).

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Overseas Visitors, October, 1961.

THE following overseas visitors will be in New South Wales in October: Dr. J. D. Llewellyn-Jones, Department of Obstetrics and Gynæcology, General Hospital, Kuala Lumpur, Malaya; Professor Hubert de Watteville, Professor of Gynæcology and Obstetrics, University of Geneva, Switzerland; Mr. Harold Dodd, Surgeon, St. Mary's Hospital Group, Paddington; Senior Surgeon, King George Hospital, Ilford, and Royal Hospital, Richmond; Surgeon, Royal London Homœopathic Hospital; Mr. W. P. Cleland, Surgeon, Brompton Chest Hospital; Thoracic Surgeon, King's College Hospital, London, and Guest Thoracic Surgeon to the Royal North Shore Hospital; Dr. Dwight E. Harken, Associate Clinical Professor of Surgery, Harvard Medical School, Boston.

Annual Subscription Course.

The following lectures are open to members of the annual subscription course.

Wednesday, October 4: 4 p.m., "The Inquiring Obstetrician —a Study of Obstetrics in Malaya", Dr. J. D. Llewellyn-Jones, Main Lecture Hall, The Women's Hospital, Crown Street.

Thursday, October 5: 11.15 a.m., "The Treatment of Eclampsia", Dr. J. D. Llewellyn-Jones, No. 1 Lecture Theatre, Blackburn Building, University of Sydney (lecture to fifth and sixth year students); 3 p.m., "Current Problems in Cardiac Surgery", Dr. Dwight E. Harken, case presentations and discussion, Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital; 8.15 p.m., "Heart Surgery—Past, Present and Future", Dr. Dwight E. Harken, Stawell Hall, 145 Macquarie Street, Sydney.

Friday, October 6: 1.15 p.m., "The Surgical Management of Angina Pectoris and Coronary Artery Disease", Dr. Dwight Harken, Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital.

Friday, October 13: 2.30 p.m., "The Problems Associated with Ventricular Septal Defects", Mr. W. P. Cleland, case demonstrations, The Royal North Shore Hospital.

Monday, October 16: 2.30 p.m., "Aortic Stenosis", Mr. W. P. Cleland, case demonstrations, The Royal North Shore Hospital.

Tuesday, October 17: 2.30 p.m., "The Surgical Treatment of Fallot's Tetralogy", Mr. W. P. Cleland, case demonstrations, The Royal North Shore Hospital.

Wednesday, October 18: 2 p.m., "Surgery of Aortic Valve Disease", Mr. W. P. Cleland, seminar, Maitland Lecture Hall, Sydney Hospital; 8.30 p.m., "Extragenital Malignant Disease Associated with Pregnancy, Including Malignant Disease of the Breast", Professor Hubert de Watteville (discussion arranged in association with the Royal Australasian College of Surgeons and the Royal College of Obstetricians and Gynæcologists), Stawell Hall, 145 Macquarie Street, Sydney.

Thursday, October 19: 5 p.m., "Fœtal Erythroblastosis", Professor de Watteville, Royal Alexandra Hospital for Children.

Monday, October 23, 8 p.m., "Fœtal Erythroblastosis", Professor de Watteville, The Royal Newcastle Hospital.

Tuesday, October 24: 1 p.m., "The Early Detection of Cervical Cancer", Professor de Watteville, Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital; 4.15 p.m., "Some Newer Developments in the Surgery of Venous Disorders of the Lower Limbs", Mr. Harold Dodd, Alfred and Mary Roberts Ward, Royal Prince Alfred Hospital; 5 p.m., "The Clinical Use of Human Pituitary Gonadotrophins", Professor de Watteville, Maitland Lecture Hall, Sydney Hospital.

Wednesday, October 25: 2 p.m., "Forceps versus Vacuum Extractor—Experience at the Maternity Hospital, Geneva", Professor de Watteville, Lecture Hall, Royal Hospital for Women; 2 p.m., "Some Newer Developments in the Surgery of Venous Disorders of the Lower Limbs", Mr. Harold Dodd, Students' Common Room, The Royal North Shore Hospital; 8.15 p.m., "The Experience of Psychoprophylactic Preparation for Painless Childbirth at the Maternity Hospital of Geneva", and "Obstetrical Analgesia with Special Reference to Continuous Peridural Anæsthesia", Professor de Watteville, Stawell Hall, 145 Macquarie Street, Sydney (arranged in conjunction with the Faculty of Anæsthetists, Royal Australasian College of Surgeons, and the Australian Society of Anæsthetists).

Thursday, October 26: 10.30 a.m., case presentations and operative demonstrations, Mr. Harold Dodd, Repatriation General Hospital, Concord; 1 p.m., "Abortion", Professor de Watteville, Students' Common Room, The Royal North Shore Hospital; 8.15 p.m., "Venous Disorders of the Lower Limbs—a Unified Concept", Mr. Harold Dodd, Stawell Hall, 145 Macquarie Street, Sydney.

Friday, October 27: 2 p.m., "The Management of Chronic Venous Ulceration", Mr. Harold Dodd, The Prince Henry Hospital.

The annual subscription course covers attendance at lectures by overseas lecturers and other specially arranged activities. The annual fee is £3 3s., from July 1. The fee for first and second year resident medical officers is £1 12s. 6d. Last-minute alterations to meetings are notified by advertisement in *The Sydney Morning Herald* ("Public Notices"), if possible on the day before the meeting.

Method of Enrolment and General Information.

Applications for enrolment on metropolitan and week-end courses should be made to the Course Secretary, Herford House, 188 Oxford Street, Paddington.

Taxation Deductions.

Fees paid by medical practitioners who are in practice for attendance at revision and week-end courses conducted by the Committee, including living and travelling expenses, are deductible (Taxation File No. AF/1865).

ROYAL PRINCE ALFRED HOSPITAL: EAR, NOSE AND THROAT DEPARTMENT.

Seminar Programme, 1961.

THE staff of the ear, nose and throat department of the Royal Prince Alfred Hospital, Sydney, will conduct a seminar on the second Saturday of every month at 8 a.m. in the Scot Skirving Lecture Theatre. The main speaker will not exceed forty minutes, and there will be a discussion at the conclusion of his remarks. All medical practitioners and clinical students are invited to attend.

At the next seminar, to be held on October 14, 1961, Dr. R. G. Mackay will speak on "Recent Trends in Rhinoplastic Surgery".

MELBOURNE MEDICAL POST-GRADUATE COMMITTEE AND UNIVERSITY OF MELBOURNE DEPARTMENT OF MEDICINE.

SYMPOSIUM ON DISORDERS OF RESPIRATORY FUNCTION.

As has been previously announced, a symposium on disorders of respiratory function will be held on October 26, 27 and 28, 1961, at the Royal Melbourne Hospital. Further financial assistance provided by C. I. G. Pty. Ltd., and by Merck Sharpe and Dohme (Aust.) Pty. Ltd., has enabled invitations to be extended to three additional contributors, two from New Zealand and one from New South Wales.

The visit of Mr. W. P. Cleland (London) now coincides with the symposium, and as a result, the joint meeting of the Victorian Laennec Society and the Victorian Cardiac Group, arranged for his visit, is now included. As was foreshadowed in the provisional programme, the symposium will now begin on Thursday, October 26, and continue until midday on Saturday, October 28. No fee will be charged for attendance, but prior registration with the Melbourne Medical Post-Graduate Committee is essential; in particular, notice is required from those requiring dinner on the evenings of Thursday and Friday, October 26 and 27. The lectures and exhibition are currently planned for the main lecture theatre and adjacent rooms, but the new hall, at present under construction in the hospital gounds, may be used. The revised and extended programme for the symposium, which is held under the auspices of the Department of Medicine, University of Melbourne, is set out below.

Thursday, October 26.

Session I: Emergency Resuscitation.

The chairman is Rear-Admiral L. Lockwood.

2.15 p.m., film: "Expired Air Resuscitation—Technique and Experimental Comparison with Other Methods" (Dr. P. Safar, U.S.A.; 50 minutes). The discussion will be opened by Dr. D. Halmagyi (Sydney). 3.20 p.m., lecture demonstration, "Emergency Resuscitation Apparatus and Training Gear", Mr. J. Osborne (C. I. G.; 15 minutes). The discussion will be opened by Dr. Russell Cole. 3.45 p.m., "Closed Chest Manual Systole", Dr. T. P. Crankshaw (10 minutes).

Session II: Drowning and Pulmonary Œdema.

The chairman is Dr. T. E. Lowe.

4.30 p.m., "Fluid in the Lungs: Therapeutic Implications of Physiological Findings", Dr. D. Halmagyi (35 minutes). The discussion will be opened by Mr. E. Allcock and Dr. J. R. Fraser. 5.30 p.m., opening of exhibits and introductory commentary: (i) equipment for intermittent positive pressure respiration, emergency resuscitation and oxygen therapy; (ii) apparatus and methods for arterial and expired gas analysis and estimation of pH; (iii) equipment used in the assessment of pulmonary function. These exhibits will remain on display throughout the Conference. 7.15 p.m., rescreening of film on "Expired Air Resuscitation".

Session III: The Pulmonary Circulation.

The chairman is Mr. C. J. Officer Brown.

8 p.m., "Physiology", Dr. D. Halmagyi (20 minutes): "Changes in Emphysema and Respiratory Failure", Dr. T. O'Donnell (20 minutes); "Special Investigations", Dr. G. Sloman (15 minutes); "Clinical Prognosis of Disorders of the Pulmonary Circulation", Dr. J. M. Gardiner (15 minutes); "Surgical Importance of Abnormalities of the Pulmonary Circulation", Mr. G. Stirling (15 minutes). The discussion will be opened by Mr. W. P. Cleland (London).

Friday, October 27.

Session IV: Panel Discussion.

The chairman is Professor Ralph Blacket (Sydney).

9.15 a.m., theme: "Morbid Anatomy, Physical Signs and Radiological Appearances: Their Relationship to Function". The subjects will be introduced by Dr. K. McLean (morbid anatomy), Dr. Blair Ritchie (physical signs) and Dr. W. S. C. Hare (radiology). The panel will include the visiting speakers.

Session V: Blood and Gas Analysis.

The chairman is Professor R. R. H. Lovell.

10.45 a.m., "Arterial Gas Analysis: Sampling and Principles of Current Techniques", Dr. B. Gandevia (10 minutes). 11 a.m., "Problems of Blood pH Determination", Dr. J. Owen (15 minutes). 11.20 a.m., "Analysis of Blood and Expired Gas": (i) "Biochemical Methods", Dr. C. Baird (15 minutes); (ii) "Instrumental Methods", Dr. John Read (Sydney), (10 minutes). 12 noon, "Rebreathing Technique for the Rapid Estimation of Arterial pCO_2", Dr. Blair Ritchie (10 minutes). 1 p.m., Royal Melbourne Hospital Resident Medical Officers' Club clinico-pathological meeting, film: "Respiratory Mechanics in Health and Disease"; Dr. John Read and Dr. P. Colville will form a panel for subsequent discussion.

Session VI: Anæsthetic Aspects of Respiratory Failure.

The chairman is Dr. Norman James.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED SEPTEMBER 9, 1961.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	2(1)	..	..	..	..	..	..	3
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	1	..	..	..	..	..	2	..	3
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	1(1)	1	..	..	..	..	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	10(3)	20(6)	1	..	..	..	4	..	35
Diphtheria	..	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	..	2	..	1	3(3)	..	1	..	7
Encephalitis	1	..	..	..	..	..	..	..	1
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	1	..	..	1
Infective Hepatitis	108(66)	46(24)	20(7)	10(4)	2(2)	11(4)	2	12	211
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	..	..	..	..	..	..	..
Malaria	..	..	1	..	..	..	..	..	1
Meningococcal Infection	..	..	..	..	..	..	..	..	..
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	7(2)	2(1)	1	..	..	..	..	..	10
Puerperal Fever	1(1)	..	..	..	..	..	..	..	1
Rubella	..	10(6)	..	..	2(1	..	..	..	12
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	8(5)	13(6)	1(1)	..	..	..	..	..	22
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	2(1)	..	..	..	..	..	2
Trachoma	..	..	..	..	..	..	..	..	..
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	24(18)	13(7)	7(3)	5(5)	6(5)	4(1)	2	1	62
Typhoid Fever	1(1)	1(1)	..	..	1(1)	..	..	..	3
Typhus (Flea-, Mite- and Tick-borne)	..	..	1(1)	..	..	..	..	..	1
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

2.15 p.m., "Pulmonary Ventilation: Methods and Assessment", Dr. H. Newman (25 minutes). 2.50 p.m., "Problems of Respiratory Anemometry", Dr. G. Kaye (10 minutes). 3.05 p.m., "End-Tidal Samples and their Significance", Dr. W. M. Crosby (10 minutes). 3.25 p.m., "Anæsthesia in Myasthenia Gravis and Allied Disorders", Dr. J. Tucker (15 minutes). 3.45 p.m., "Anæsthesia in Emphysematous Subjects", Dr. P. Currie (20 minutes).

Session VII: Diffuse Pulmonary Disease Other than Emphysema.

The chairman is Dr. Eric Clarke.

4.45 p.m., "Clinical Features and Functional Patterns", Dr. B. Gandevia (15 minutes). 5 p.m., "Diffusion Defects and Their Assessment", Dr. J. D. Sinclair (New Zealand) (25 minutes). 5.30 p.m., "Ventilation-Perfusion Relationships", Dr. John Read (20 minutes). 5.50 p.m., "Circulatory Aspects", Dr. T. O'Donnell (10 minutes). The discussion will be opened by Dr. Murray Maxwell. 7.15 p.m., rescreening of film on "Respiratory Mechanics".

Session VIII: Emphysema.

The chairman is Professor Ralph Blacket (Sydney).

8 p.m., "Pathogenesis of Respiratory Failure", Dr. John Read (30 minutes); "Mechanical Abnormalities in Emphysema", Dr. Alistair Campbell (15 minutes). The discussion will be opened by Dr. J. D. Sinclair.

9 p.m., "Management of Respiratory Failure": (i) "Principles and General Measures", Dr. B. Gandevia (15 minutes); (ii) "Oxygen Therapy and Assisted Respiration", Dr. John Read (15 minutes).

Saturday, October 28.

Session IX: Respiratory Paralysis.

The chairman is Dr. H. McLorinan.

9.30 a.m., lecture demonstration, "A Comparison of the Bird and Bennett Respirators", Mr. F. S. Biggs (C.I.G.) (25 minutes). The discussion will be opened by Dr. Ralph Clark. 10.30 a.m., "Poliomyelitis and Quadriplegia": (i) "Physiological Aspects of Respiration", Dr. Peter Colville (20 minutes); (ii) "Respiratory Aspects of Management", Dr. Noel Bennett (15 minutes). 11.15 a.m., "Tetanus: Management from the Respiratory Viewpoint", Dr. P. Wilson (15 minutes). The discussion will be opened by Dr. Nigel Gray.

Notes and News.

Pfizer Corporation Appointments.

In consequence of the appointment of Mr. P. G. Sheridan as Regional Manager of the Pfizer Australasian-Indonesian geographic area with headquarters in Sydney, Dr. K. N. Gollan has been appointed General Manager of Pfizer Corporation, Australia.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Fairbairn, Thomas Douglas Gilfillan, M.B., Ch.B., 1942 (Univ. of St. Andrews), Western Highway, Springwood, N.S.W.

Deaths.

THE following deaths have been announced:

MAKIN.—Frank Humphrey Makin, on September 20, 1961, at Adelaide, South Australia.

CHAMPAIN.—John Vance Champain, on September 21, 1961, at Tenterfield, N.S.W.

CONLON.—Alfred Austin Conlon, on September 21, 1961, at North Sydney, N.S.W.

ACCOLA.—James Bernhard Accola, on September 22, 1961, at Sydney, N.S.W.

Diary for the Month.

OCTOBER 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee; Organization and Science Committee.
OCTOBER 12.—New South Wales Branch, B.M.A.: Public Relations Committee.
OCTOBER 13.—Queensland Branch, B.M.A.: Council Meeting.
OCTOBER 16.—Victorian Branch, B.M.A.: Finance Sub-Committee.
OCTOBER 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.
OCTOBER 18.—Western Australian Branch, B.M.A.: General Meeting.
OCTOBER 19.—New South Wales Branch, B.M.A.: Clinical Meeting.
OCTOBER 19.—Victorian Branch, B.M.A.: Executive Meeting of Branch Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): Medical Officers to Sydney City Council. All contract practice appointments in New South Wales. Members are requested to consult the Medical Secretary before undertaking practice in dwellings owned by the Housing Commission.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full data in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: 68-2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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